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RESEARCH REFERENCE

Prepared August 2026

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HYPOCHLOROUS ACID

WHO 2025 Essential Medicines review, committee recommendation and complete source report

WHO COMMITTEE OUTCOME

Explicit EML and EMLc listing recommended for aqueous hypochlorous acid at ≥150 ppm as an **environmental disinfectant**.

The report did not recommend listing for topical antisepsis or wound care because the evidence for benefit was considered inconclusive.

SOURCE

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What the WHO report says

A concise reading of the hypochlorous acid section in the 2025 report of the 25th WHO Expert Committee.

RECOMMENDED

Environmental disinfection

Explicit EML/EMLc listing for aqueous HOCl containing ≥150 ppm.

NOT RECOMMENDED

Topical antisepsis and wound care

The Committee cited inconclusive evidence for benefit and no new evidence versus 2021.

Evidence discussed in the report

- Laboratory and clinical evidence spanning environmental disinfection, skin decolonization, antisepsis and wound care.
- Studies involving MRSA, high-risk HPV, dialysis catheter infections, surgical wounds, diabetic foot ulcers and venous leg ulcers.
- Safety discussion distinguishes pure, controlled HOCl formulations from higher-pH or mixed-oxidant/hypochlorite formulations.
- The application presented no cost-effectiveness data; the Committee also noted the lack of new benefit and harm evidence compared with 2021.

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WHO Technical Report Series

1064

The selection and use of essential medicines

Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2025 (including the 24th WHO Model List of Essential Medicines and the 10th WHO Model List of Essential Medicines for Children)

World Health Organization

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Executive summary

The meeting of the 25th WHO Expert Committee on the Selection and Use of Essential Medicines took place at WHO headquarters in Geneva, Switzerland, from 5 to 9 May 2025. The aim of the meeting was to review and evaluate applications for the 24th WHO Model List of Essential Medicines (EML) and the 10th WHO Model List of Essential Medicines for Children (EMLc) (the Model Lists).

Essential medicines are those that satisfy the priority health-care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost–effectiveness. They are intended to always be available in functioning health systems, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford.

The WHO Model Lists are updated every 2 years and are intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. Selection of a limited number of medicines as essential, taking into consideration national disease burden and clinical need, can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use, and lower costs for both health-care systems and patients.

The Expert Committee considered a total of 59 applications, including 31 proposals for the addition of new medicines or medicine classes, 10 proposals for new indications for currently listed medicines, three proposals for the addition of new formulations of currently listed medicines, one proposal for the removal of a currently listed medicine, and 14 other applications relevant to the Model Lists and the WHO AWaRe classification of antibiotics. In accordance with procedures endorsed by the 109th Executive Board in the Report by the Secretariat EB109/8 in 2001, the Expert Committee reviewed and evaluated the scientific evidence for the effectiveness, safety, and comparative cost and cost–effectiveness of the medicines in question.

In summary, the Expert Committee:

- recommended the addition of 20 new medicines to the EML (16 to the core list and four to the complementary list);
- recommended the addition of 15 new medicines to the EMLc (12 to the core list and three to the complementary list);
- recommended adding additional indications for seven currently listed medicines;
- recommended the addition of new formulations of 19 medicines on the EML and of 49 medicines on the EMLc;
- recommended the deletion of three medicines from the EML and four medicines from the EMLc and the deletion of specific formulations of a further 20 medicines from the EML and 29 medicines from the EMLc; and
- did not recommend proposals for the addition of new medicines or new indications for 24 medicines or medicine classes.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 523 (from 502 in 2023), including 374 on the EMLc (from 361 in 2023). These totals do not include medicines recommended on the Model Lists as therapeutic alternatives.

Changes to the Model Lists are shown in Tables 1–3. Applications for proposed changes to the Model Lists that were not recommended are shown in Table 4. Changes to the AWaRe classification of antibiotics are shown in Table 5.

The Expert Committee's recommendations are briefly described in this document.

All applications and documents reviewed by the Expert Committee are available on the WHO website (*1*).

Section 1: Anaesthetics, preoperative medicines and medical gases

Section 1.1.1 Inhalational medicines

The Expert Committee recommended:

- the removal of halothane from the EML and EMLc to reinforce the importance of prioritizing alternative inhalational anaesthetic agents (e.g. sevoflurane);
- the inclusion of a note with the listing of nitrous oxide on the EML and EMLc about the preferred supply via point-of-care cylinders instead of centrally supplied (piped) delivery systems.

The Expert Committee recognized that halothane and nitrous oxide are potent greenhouse gases and ozone-depleting substances with significant environmental consequences. These recommendations support efforts to reduce the impact of essential anaesthetic gases on climate change. The Expert Committee considered that substitution of halothane with alternatives that have a lower propensity for environmental impact (e.g. sevoflurane) while delivering high-quality care is an important action for health-care systems. Equally, minimizing system waste by adopting a nitrous oxide waste reduction strategy and transitioning to point-of-care cylinders from centrally piped infrastructure should be encouraged in national health-care systems.

Section 5: Medicines for neurological disorders

The Expert Committee endorsed changes to the structure of Section 5 of the Model Lists, incorporating the suggestions made by Médecins Sans Frontières in its contribution received during the public consultation period. Additional changes to this section after other recommendations made during the meeting are also endorsed. The changes are summarized in Table 3.

Section 5.1 Medicines for central nervous system disorders and infections

The Expert Committee did not recommend the inclusion of risdiplam on the EML and EMLc for use in the treatment of spinal muscular atrophy at this time. As was the case when an application for risdiplam was considered by the 2023 Expert Committee, the Committee noted that greater

benefits of treatment in terms of motor function were observed in younger children. In particular, the Committee noted the preliminary reporting of positive and relevant outcomes from the RAINBOWFISH trial in presymptomatic infants, but that the trial results have to date only been reported in a conference presentation and have not yet been evaluated by the clinical and scientific community and published in a peer-reviewed journal. As such, the internal and external validity of the results could not be fully assessed by the Expert Committee due to limited available information. The Committee requested that a further update be sought in a resubmission to the 2027 Expert Committee meeting, with the latest published RAINBOWFISH trial results. The Committee also considered that if the preliminary results of the 24-month follow-up of the RAINBOWFISH trial are confirmed for patient-important outcomes (e.g. ability to sit without support, reduced need for respiratory support), if the risk of bias associated with the trial is low, if eligible presymptomatic patients can be identified, and if no evidence emerges against the use of risdiplam in this population (e.g. serious safety concerns), then a positive recommendation to include risdiplam on the EMLc could be possible in the future.

Section 5.1.1 Antiseizure medicines

The Expert Committee recommended extending the listing for prednisolone on the EMLc to include the new indication of infantile epileptic spasms syndrome, based on clinical need, evidence of favourable effectiveness and safety, lower costs and better cost–effectiveness than alternative first-line treatment options.

Section 5.1.4 Medicines for cerebral palsy

The Expert Committee recommended the addition of intrathecal baclofen to the EML and EMLc for the treatment of spasticity associated with cerebral palsy based on evidence of a favourable balance of efficacy and harms. Oral baclofen was also recommended for addition in recognition of its use: to assess responsiveness to intrathecal therapy before surgery to install the administration pump; as a complementary therapy during the intrathecal dose titration when the pump is installed; as supportive therapy when intrathecal baclofen therapy is discontinued; and to prevent and treat baclofen withdrawal, which can be severe and life-threatening.

Section 5.1.5 Medicines for headache disorders

The Expert Committee did not recommend the inclusion of carbamazepine for the new indication of trigeminal neuralgia because the available clinical evidence was of insufficient quality and therefore confidence in the reported benefits and harms was limited.

Section 5.1.5.1 Medicines for acute migraine attacks

The Expert Committee recommended the addition of eletriptan, ibuprofen and naproxen to the EML for acute treatment of migraine based on evidence of favourable benefit-to-harm profiles, and the possibility of increasing the choice of medicines for acute migraine for patients, while maintaining a parsimonious number of options at the pharmacological class level. Naproxen is listed as a therapeutic alternative to ibuprofen and eletriptan is listed as a therapeutic alternative to sumatriptan under square box listings.

Section 5.1.5.2 Medicines for migraine prophylaxis

The Expert Committee did not recommend the inclusion of amitriptyline or bisoprolol for migraine prophylaxis due to inadequate evidence for relative benefit compared with currently listed propranolol. The Committee did not recommend the inclusion of fremanezumab for prophylaxis of high-frequency or chronic migraine. The Committee considered that fremanezumab demonstrated favourable outcomes compared with placebo. However, the absence of direct comparative evidence for fremanezumab versus currently listed propranolol and the resultant uncertainty about the relative benefit made it impossible to adequately justify the substantial cost difference between the two medicines.

Section 5.1.5.3 Medicines for cluster headache

The Expert Committee recommended the inclusion of sumatriptan, prednisolone and verapamil in the EML for the acute treatment and prophylaxis of cluster headache based on a favourable balance of benefits to harms, while also noting the key role of rapid-flow oxygen for this indication.

Section 6: Anti-infective medicines

Section 6.1.2 Antifilarials

The Expert Committee recommended the inclusion of moxidectin on the EML and EMLc as a therapeutic alternative to ivermectin for treatment of onchocerciasis and lymphatic filariasis based on evidence of a favourable balance of benefits to harms.

Section 6.1.3 Antischistosomals and other antitrematode medicines

The Expert Committee recommended the addition of arpraziquantel, a dispersible or orodispersible tablet, on the EMLc for the treatment of schistosomiasis in preschool-aged children based on evidence of similar efficacy and safety when compared with praziquantel. The Committee recognized the medical need for a more palatable, easy-to-administer paediatric formulation of praziquantel and the efforts to develop innovative orodispersible tablet formulations for praziquantel for paediatric use. The Committee noted that arpraziquantel is the active enantiomer of praziquantel. The Committee considered that the proposed formulation was age-appropriate for the target population, allowed precise dosing of children and infants of different body weights and had better palatability and acceptability than praziquantel for this age group. Listing is recommended for arpraziquantel as a therapeutic alternative to praziquantel (which remains the class representative) under a square box listing.

Section 6.2.3 Reserve group antibiotics

The Expert Committee did not recommend the inclusion of imipenem + cilastatin + relebactam for the treatment of infections caused by multidrug-resistant organisms for the same reasons as given by the previous Expert Committee: imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally; and other reserve antibiotics with a similar spectrum of activity are already included on the Model Lists. However, the Committee advised that future evaluation of

an application for inclusion of imipenem + cilastatin + relebactam on the Model List could be considered following any changes to the definition of the AWaRe Reserve category arising from the planned revision (see Other matters considered by the Expert Committee).

Section 6.2.5 Antituberculosis medicines

The Expert Committee recommended the inclusion of a dispersible tablet formulation of rifapentine 150 mg on the EMLc for use in tuberculosis preventive treatment regimens in children in accordance with recommendations in WHO guidelines.

The Committee recommended the removal of the footnote on limiting the use of rifabutin to patients with human immunodeficiency virus (HIV) receiving protease inhibitors and the transfer the listings of medicines used in multidrug-resistant tuberculosis from the complementary (e.g. secondary care level) to the core list (e.g. primary care level).

Section 6.4.2 Antiretrovirals

The Expert Committee recommended the inclusion of a fixed-dose combination dispersible tablet formulation of abacavir + dolutegravir + lamivudine on the EMLc for the treatment of children with HIV in accordance with recommendations in WHO guidelines.

Section 6.4.3 Other antivirals

The Expert Committee recommended the removal of ribavirin from the EML and EMLc as a treatment for viral haemorrhagic fevers. The Committee noted how the interpretation of evidence supporting ribavirin for viral haemorrhagic fevers has shifted significantly since the 1980s. Ribavirin was recommended as a routine treatment based largely on a quasi-experimental study conducted during that time, which suggested potential benefits, particularly in Lassa fever. However, that early evidence was methodologically unsatisfactory, with substantial risks of bias, including lack of randomization, small sample sizes and inadequate control groups. Over time, as standards for evaluating clinical interventions have become more rigorous, the limitations of the original evidence have become more apparent. Recent reviews have highlighted the lack of high-quality randomized controlled trials and have raised concerns about the potential for harm, such as haemolytic anaemia and other adverse effects. The Committee noted that WHO guidance for the clinical management of viral haemorrhagic fevers is currently under development and it is expected that ribavirin treatment will be recommended only within the context of clinical trials to evaluate safety and efficacy.

Section 6.5.5 Antitrypanosomal medicines

The Expert Committee recommended extending the listing for fexinidazole on the EML and EMLc to include the new indication of treatment for first- and second-stage human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* in adults and children aged 6 years and older based on evidence of effectiveness and safety compared with alternative treatments. Compared with suramin (for first stage) or melarsoprol (for second stage), fexinidazole is the preferred treatment for both stages of the disease, is administered orally and it is not associated with fatal reactive encephalopathy, a rare but severe and often deadly complication of melarsoprol.

Section 7: Medicines for cystic fibrosis

The Expert Committee recommended the inclusion of elexacaftor + tezacaftor + ivacaftor fixed-dose combination and single-agent ivacaftor on the core list of the EML and EMLc for the treatment of cystic fibrosis in people aged 2 years and older with at least one F508del mutation or another responsive cystic fibrosis transmembrane conductance regulator (CFTR) mutation based on evidence of a favourable balance of benefits to harms. The Committee acknowledged the relevant benefits across multiple outcomes, including improvement in lung function, reduction in pulmonary exacerbations due to infections or inflammation, improvements in quality of life and potential to prevent or at least delay long-term complications, including premature death. The Committee recognized that the evidence supporting use of elexacaftor + tezacaftor + ivacaftor is solid, as it originates from multiple high-quality randomized controlled trials and post-approval observational studies confirm the effectiveness and safety in more populations than those enrolled in trials. The Committee noted that elexacaftor + tezacaftor + ivacaftor therapy is effective for most patients with cystic fibrosis, significantly expanding the cohort of patients that can benefit from this therapy compared with earlier CFTR modulators, which only benefited smaller subgroups. The Committee acknowledged the high cost and limited availability of the medicines but considered that inclusion could support efforts to expand regulatory approval across countries, stimulate development of generics and promote equitable access and affordability. Listing is recommended in a new section of the Model Lists for medicines for cystic fibrosis.

Section 8: Immunomodulators and antineoplastics

Section 8.2.1 Cytotoxic medicines

The Expert Committee did not recommend the inclusion of temozolomide on the EML and EMLc for the treatment of high-grade glioma (as monotherapy), relapsed or refractory high-risk neuroblastoma (in combination with irinotecan or topotecan), relapsed Ewing sarcoma (in combination with irinotecan), or as monotherapy for treatment of other relapsed or refractory paediatric solid tumours as palliative treatment. The Committee noted that temozolomide has not been demonstrated to improve survival in patients with neuroblastoma or Ewing sarcoma and, while the medicine has shown a small survival benefit in some patients with high-grade glioma, the evidence is limited. Temozolomide is also associated with an increased risk of severe haematological toxicity. Thus, the Committee considered that the balance of benefit to harm was not favourable.

Section 8.2.2 Targeted therapies

The Expert Committee did not recommend the inclusion of panitumumab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), on the EML for the treatment of KRAS wild-type metastatic colorectal cancer based on evidence of limited survival benefit and risk of harms. The Committee noted that the overall survival benefit in the second- and third-line settings was below the established threshold for EML eligibility (i.e. a minimum overall survival benefit of 4–6 months). In the first-line setting the overall survival benefit was modest and not consistent across all patients and may be influenced by factors such as tumour location and additional *RAS*/*BRAF*

mutations. The Committee noted the need to exclude patients with RAS mutations, given that the addition of panitumumab to chemotherapy in this population has been shown to decrease overall survival. The Committee also noted substantial toxicities.

The Expert Committee recommended the inclusion of zanubrutinib, a Bruton tyrosine kinase inhibitor, on the EML for the treatment of relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma based on evidence of a survival advantage compared with chemo-immunotherapy, and a similar survival benefit to that previously observed for ibrutinib, with fewer side-effects (e.g. less atrial fibrillation and bleeding in some trials). Evidence in the first-line setting is promising but is not yet as well established as in the relapsed or refractory setting. An application presenting the evidence for this class of medicines in the first-line treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma is encouraged for 2027. Listing is recommended for zanubrutinib as a therapeutic alternative to ibrutinib (which remains the class representative) under a square box listing. The Committee acknowledged that ibrutinib remains highly priced in most countries. Ibrutinib may face competition from newer-generation Bruton tyrosine kinase inhibitors such as zanubrutinib, which is more accessible in some countries, has a better domestic cost–effectiveness profile and potentially could better align with local medicine policy priorities.

Section 8.2.3 Immunomodulators

The Expert Committee recognized that cancer is a growing societal, public health and economic problem globally and is responsible for nearly one in three premature deaths from noncommunicable disease. The proportion of patients with advanced stage at first presentation is still substantial. Solid tumours that are amenable to effective therapy using programmed cell death protein 1/programmed cell death ligand-1 (PD-1/PD-L1) immune checkpoint inhibitors are major causes of the rising burdens with respect to lives lost and cost of management. The Committee noted the rapid pace of innovation in immuno-oncology and emphasized the importance of reducing inequities in cancer care by increasing access to immune checkpoint inhibitors, among other strategies.

In consideration of the application proposing inclusion on the EML of multiple PD-1/PD-L1 immune checkpoint inhibitors for multiple cancer indications, the Expert Committee:

- appreciated the approach taken by the WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies at the University of Cologne, Germany to identify the PD-1/PD-L1 immune checkpoint inhibitor–indication pairings proposed for EML listing from among the many approved and available, and noted that the approach was up-to-date, comprehensive, systematic, transparent and evidence-based and provided a solid basis for its decision-making;
- noted that all proposed pairings were approved by the European Medicines Agency for the first-line treatment of adults for the therapeutic indications for which they are proposed, had evidence from randomized trials, and received a score of four or higher on the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale in the non-curative setting;

- applied the EML principle for cancer medicines to demonstrate at least 4–6 months overall survival gain in randomized controlled trials;
- appreciated and took into consideration the review of the application by the EML Cancer Experts group and the evidence-to-decision frameworks that followed the GRADE approach prepared by the Secretariat.

The Committee favoured pairings where the evidence strongly supported a large benefit-to-risk ratio. The Committee considered monotherapy more positively than combination therapy for indications where both are approved and a trade-off between additional efficacy, toxicity and cost would typically occur.

The Expert Committee recommended the inclusion of the following immune checkpoint inhibitors on the EML:

- pembrolizumab, atezolizumab and cemiplimab as first-line monotherapy of metastatic non-small cell lung cancer with ≥ 50% PD-L1 expression, listing pembrolizumab with a square box as class representative and atezolizumab and cemiplimab as specified therapeutic alternatives;
- pembrolizumab as first-line monotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer;
- pembrolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic cervical cancer with ≥ 1% PD-L1 expression.

The Committee considered that these recommendations for inclusion provide the best chance at minimizing financial burden and concentrating expenditure in the areas with the most favourable incremental gain in benefit-to-risk ratio. The Committee noted that use of immune checkpoint inhibitors in adults with solid tumours that have predictive biomarkers (e.g. high PD-L1 expression for non-small cell lung cancer) rather than all patients is the highest priority to enable greater access in settings where budgetary constraints may require prioritization of scenarios that offer the greatest clinical value.

With the recommendation to list pembrolizumab for the above-mentioned indications, the Committee recommended changing the current square box listing of nivolumab as the class representative and pembrolizumab as a specified therapeutic alternative for metastatic melanoma, to make pembrolizumab the class representative with nivolumab as specified therapeutic alternative. This is intended to signal to countries the possibility of aggregating procurement of a single molecule, pembrolizumab, across multiple cancer indications and influencing price negotiations with manufacturers. Limiting procurement fragmentation by focusing on a select few immune checkpoint inhibitors is likely to facilitate central purchasing through competitive tendering and better competition from pembrolizumab biosimilars, thereby increasing access.

In addition to its recommendations on which immune checkpoint inhibitors to prioritize for inclusion on the EML, the Committee also recognized the value and recommended the use of strategies to improve access, particularly in resource-constrained settings, as presented in the report

from the EML cancer experts consultation meeting. The Committee noted that these strategies were based on evaluation of available evidence and pragmatic considerations. The Committee considered the strategies to improve access to care had two components: clinical strategies and health system strategies. The Committee acknowledged that while clinical strategies (over which doctors and patients have greater control) and health system strategies (requiring government-led policy legislations and reforms) should complement each other, clinical strategies can be implemented immediately, thereby delivering rapid benefits for access.

Clinical strategies – doctors and patients. The Committee acknowledged the importance of empowering patients to make an informed and consensual decision about their treatment, including information on benefits, harms, accessibility and feasibility of care. This might require comparing alternatives that differ from each other in one or more of the aforementioned dimensions. Strategies that can improve access include: dose optimization according to patient weight (weight-based dosing); rounding down doses to the closest vial size and strength (dose banding); or hybrid dosing regimens that combine the two; and, if relevant, vial sharing. Additionally, longer intervals between treatment administration or shorter durations of treatment can be considered. The Committee also noted that ongoing studies were investigating outcomes with ultra-low dose immunotherapy. If the results are favourable, ultra-low dose immunotherapy could be a viable strategy to further improve access.

Health system strategies – policy-makers. To enable better value procurement through tendering and competition leading to increased access for individuals and health systems, the Committee recommended that national policies should take advantage of similar clinical performance among different immune checkpoint inhibitors, regardless of their biological target (i.e. PD-1 or PD-L1). The Committee opted to recommend four immune checkpoint inhibitors for non-small cell lung cancer using the square box listing, indicating interchangeability at the health system level for this indication. The recommended medicines have different pharmacological properties but are considered therapeutic alternatives. Where there is no relevant difference in terms of efficacy and safety data, the preferred medicine at the country level should be the one that is generally available at the lowest price. At the country level, the interpretation of the square box should be extensive (i.e. a class effect), potentially covering other equally effective and safe immune checkpoint inhibitors of assured quality where these are offered at an advantageous price.

The Committee also recommended that quality-assured biosimilars of the listed immune checkpoint inhibitors be considered therapeutic alternatives to the corresponding reference medicine (even if not yet available), to signal to countries the importance of strategies to encourage rapid entry of biosimilars into markets.

The Committee recognized the need for companion in-vitro diagnostic tests to identify patients eligible for treatment with the recommended immune checkpoint inhibitors. The Committee noted that access to diagnostic capacity is limited in less-resourced settings and may be a barrier to appropriate and optimal use of these medicines. However, the Committee highlighted that this limited capacity is more variable in middle-income countries, where testing for molecular alterations is more readily available and the price associated with tests is a small fraction of the price associated with treatment. The Committee recognized that the requirement for companion

diagnostics adds additional cost but offers a pathway to limit inappropriate use of immune checkpoint inhibitors (i.e. outside of recommended indications) and serves to prevent the waste of resources with non-essential or lower-value use.

The Committee considered that countries can apply their own affordability criteria to determine which (if any) of the recommended immune checkpoint inhibitors can be reasonably incorporated into national EMLs and reimbursement schemes. In addition, the Committee considered that countries can apply their own feasibility criteria in assessing health system readiness for implementing immune checkpoint inhibitors, in terms of diagnostic infrastructure, health-care worker training in immuno-oncology, resources for the management of immune-mediated side-effects and monitoring capabilities, to ensure their safe and effective use.

The Expert Committee did not recommend listing for the following immune checkpoint inhibitors:

- cemiplimab, durvalumab plus tremelimumab, nivolumab plus ipilimumab, or pembrolizumab – each in combination with chemotherapy – for the treatment of oncogenic-driver wild-type metastatic non-small cell lung cancer regardless of PD-L1 expression;
- tislelizumab in combination with chemotherapy for oncogenic-driver wild-type metastatic non-small cell lung cancer with ≥ 50% PD-L1 expression;
- nivolumab plus ipilimumab for the treatment of dMMR/MSI-H phenotype metastatic colorectal cancer or metastatic melanoma;
- dostarlimab in combination with chemotherapy for dMMR/MSI-H phenotype metastatic endometrial cancer;
- pembrolizumab or nivolumab, in combination with chemotherapy, for first-line treatment of metastatic ERBB2-negative gastric or gastro-oesophageal junction adenocarcinoma with ≥ 1% or ≥ 5% PD-L1 expression, respectively;
- durvalumab in combination with chemotherapy for first-line treatment of biliary tract cancer regardless of PD-L1 expression;
- durvalumab monotherapy, durvalumab plus tremelimumab, or atezolizumab plus bevacizumab for first-line treatment for metastatic hepatocellular carcinoma regardless of PD-L1 expression;
- pembrolizumab in combination with chemotherapy for first-line treatment of metastatic head and neck squamous cell carcinoma;
- pembrolizumab, nivolumab, or nivolumab + ipilimumab – each in combination with chemotherapy – for first-line treatment of metastatic oesophageal squamous cell cancer;
- nivolumab + ipilimumab, pembrolizumab + axitinib, or pembrolizumab + lenvatinib for the first-line treatment of metastatic renal cell carcinoma regardless of PD-L1 expression;

- pembrolizumab in combination with chemotherapy for first-line treatment of triple-negative breast cancer with combined positive score (CPS) ≥ 10.

Reasons not to recommend inclusion of these pairings included prioritization of monotherapy over combination therapy, magnitude of overall survival gains of less than 4–6 months, limited or absence of mature overall survival data, unfavourable benefit-to-risk profiles, uncertainty about optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (i.e. in sequence or in combination), and uncertainty about optimal use across different patient cohorts which may vary with the immunogenicity of tumour types.

The Expert Committee did not recommend the inclusion of tislelizumab or toripalimab on the EML for the treatment of oesophageal squamous cell carcinoma at this time. In the first-line setting, the Committee considered that the reported overall survival gains offered by these medicines were relatively consistent (suggesting that these medicines could be considered therapeutic alternatives). However, the Committee judged the overall survival gains to be moderate in size and that the benefit of these gains was offset by the unclear role of PD-L1 expression as a predictive biomarker. The Committee also noted the potential for increased harm in patients with poorer prognosis at baseline and the lack of mature overall survival data. In the second-line setting, the Committee noted that the magnitude of benefit was smaller compared with the first-line setting and did not meet the established 4–6-month threshold.

The Expert Committee did not recommend the inclusion of toripalimab on the EML for the treatment of nasopharyngeal carcinoma. The Committee considered that toripalimab in combination with chemotherapy showed promising overall survival gains compared with chemotherapy alone in the first-line setting but noted that benefit in the second-line setting was more limited. The Committee also noted that trials of other immune checkpoint inhibitors are ongoing in nasopharyngeal carcinoma. The Committee emphasised that the maturation of additional data, in the context of all immune checkpoint inhibitors approved for nasopharyngeal carcinoma, especially concerning overall survival and quality of life, will be pivotal to inform judgements on whether to include toripalimab on the EML in the future.

The Expert Committee recommended the inclusion of blinatumomab on the EML and EMLc for the treatment of CD-19-positive B-lineage acute lymphoblastic leukaemia based on compelling evidence from randomized clinical trials showing the superiority of blinatumomab over chemotherapy in meaningfully improving: (i) survival in children, adolescents and adults with relapsed B-lineage acute lymphoblastic leukaemia; and (ii) survival in adults with B-lineage acute lymphoblastic leukaemia in the front-line setting; and (iii) disease-free survival in children with B-lineage acute lymphoblastic leukaemia in the front-line setting. Blinatumomab is associated with fewer grade ≥ 3 adverse events compared with chemotherapy but has specific adverse events that would require specialist management and may represent a barrier to implementation in most low-resource settings. Blinatumomab is available as an intravenous formulation. It requires continuous infusion over 28 days per cycle to maintain stable plasma levels due to its very short half-life (about 2 hours). This continuous exposure is crucial to maintain therapeutic efficacy and minimize cytokine release syndrome. The limited feasibility of blinatumomab should be contrasted against the limited feasibility of the comparator – standard chemotherapy – which

involves highly toxic, multi-agent regimens over an extended period. In both paediatric and adult patients, standard chemotherapy requires frequent hospitalizations and supportive care, including for long-term sequelae of prolonged myelosuppression.

Overall, the Committee considered that the balance of benefit to harm of blinatumomab was strongly favourable in a disease where clinical cure is a realistic goal. The Committee noted the current high cost of blinatumomab treatment and that, while it has been determined to be cost-effective in some high-income settings, cost–effectiveness studies in other settings have given variable results, depending on patient population and line of therapy. In considering the feasibility of implementing blinatumomab, the Committee recognized that countries in resource-limited settings considering including blinatumomab on their national EMLs must consider their capacity to ensure the requirements for safe administration, management of adverse events and local prioritization of implementation with respect to age and line of treatment.

Section 8.2.5 Supportive medicines

The Expert Committee did not recommend the expansion of the indications for erythropoiesis stimulating agents (e.g. epoetin alfa) on the EML and EMLc to include supportive management of chemotherapy-induced anaemia, based on an unfavourable and uncertain long-term benefit-to-harm profile. The Committee noted that judicious use of erythropoiesis-stimulating agents in patients receiving chemotherapy improves haemoglobin levels, may reduce transfusion requirements and may be associated with improvements in quality of life. However, they have not been shown to improve overall survival, with some clinical studies reporting inferior survival and worse cancer outcomes, as these medicines might stimulate tumour growth directly or affect the tumour microenvironment. The Committee also noted that guidelines from professional societies (e.g. the American Society of Clinical Oncology and the European Society of Medical Oncology) recommend careful patient selection and informed consent about risks and conservative dosing, factors that are important limitations to the feasibility of the use of this class of medicines in this context.

Section 10: Medicines affecting the blood

Section 10.2 Medicines affecting coagulation

The Expert Committee recommended the inclusion of emicizumab on the EML and EMLc for prophylactic treatment of haemophilia A with and without factor VIII (FVIII) inhibitors based on a favourable balance of benefits to harms. The Committee also made some important remarks on the implementation of the recommendation depending on the level of available resources. In recognition of the current high price of emicizumab, the Committee highlighted that the value of emicizumab prophylaxis is greatest in people with haemophilia A with FVIII inhibitors, in whom factor replacement is ineffective. In people with severe haemophilia A without FVIII inhibitors, prophylaxis with plasma-derived or recombinant FVIII may be a better value, more affordable treatment option. In considering the inclusion of emicizumab on national EMLs in resource-limited settings, and in line with national needs, decision-makers may wish to prioritize/limit selection and use of emicizumab in the first instance to the population of people

with haemophilia A with FVIII inhibitors. Selection and use could be extended to people with severe haemophilia A without inhibitors when the price of emicizumab is lowered and/or if resources allow.

The Expert Committee recommended the inclusion of phytomenadione mixed micelle solution formulation on the EML and EMLc for the management of haemorrhage due to severe hypoprothrombinaemia, and on the EMLc for the prophylaxis and treatment of haemorrhagic disease of the newborn. The Committee considered that the proposed formulation is an additional effective treatment option that offers flexibility for administration, with evidence of comparable efficacy and safety as currently listed formulations.

Section 10.3 Medicines for haemoglobinopathies

The Expert Committee endorsed the proposed changes to Section 10.3 of the Model Lists made by the Secretariat, incorporating the suggestions made by the WHO Department of Maternal, Newborn, Child and Adolescent Health, and Ageing to title the section "Medicines for haemoglobinopathies" and to transfer the listing of hydroxyurea (hydroxycarbamide) from the complementary to the core list.

Section 11: Blood products, coagulation factors, and plasma substitutes

Section 11.1 Blood and blood components

The Expert Committee recommended that non-pathogen-reduced (i.e. native) cryoprecipitate and pathogen-reduced cryoprecipitate be removed from the Model Lists for use in prophylactic treatment of haemophilia A and von Willebrand disease. The Committee recognized the increased risks of transfusion-transmitted infections associated with repeated transfusions in patients with these conditions.

The Expert Committee recommended that non-pathogen-reduced (i.e. native) cryoprecipitate be retained on the EML and EMLc as a therapeutic alternative to pathogen-reduced cryoprecipitate for use in cases of life-threatening major haemorrhage and rapid loss of blood volume (e.g. severe trauma, major surgery, obstetric haemorrhage). The Committee considered that at this time and under the aforementioned clinical circumstances, native cryoprecipitate still represents a therapeutic alternative to coagulation factors or pathogen-reduced cryoprecipitate when these are not available. In such situations, the iatrogenic risks are clearly outweighed by the potential life-saving benefits of native cryoprecipitate. The Committee recognized the importance of preferential use of pathogen-reduced cryoprecipitate over native cryoprecipitate due to the reduced risk of transfusion-transmitted infections. However, the Committee noted that widespread global access to pathogen-reduced cryoprecipitate is currently limited. In settings where pathogen-reduced cryoprecipitate is not available, native cryoprecipitate is a last resort alternative.

The Expert Committee recommended that the current listings for plasma-derived coagulation factors VIII and IX be transferred from the complementary to the core list of the EML and EMLc.

For consistency across listings for other medicines used in the treatment of haemophilia and von Willebrand disease, the Committee recommended that the listing for desmopressin also be transferred from the complementary to the core list.

The Expert Committee recommended the removal of coagulation factor IX complex as a therapeutic alternative under the square box listing of plasma-derived coagulation factor IX on the EML and EMLc given the increased risk of thrombosis associated with this product.

Section 11.3 Coagulation factors

The Expert Committee recommended the inclusion of recombinant coagulation factor VIII for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia A, and of recombinant coagulation factor IX for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia B to the core list of the EML and EMLc. The recommendation is made based on evidence of equal effectiveness to plasma-derived coagulation factors for outcomes including reduced bleeding rates, percentage of patients without bleeding events, improved joint health scores and improved health-related quality of life measurement scores. Compared with plasma-derived coagulation factors, recombinant coagulation factors are not associated with an increased risk of bloodborne virus transmission. Nevertheless, the Committee recognized that plasma-derived coagulation factors continue to represent an important treatment option, may offer advantages over recombinant products in the context of inhibitor development and may be more affordable in some settings.

Section 12: Cardiovascular medicines

Section 12.3 Antihypertensive medicines

The Expert Committee recommended the inclusion of triple fixed-dose combination antihypertensive formulations containing an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, a long-acting dihydropyridine calcium channel blocker and a thiazide or thiazide-like diuretic on the EML based on a favourable balance of benefits to harms in patients with uncontrolled blood pressure on dual therapy or in high-risk patients (e.g. with diabetes, kidney disease, cardiovascular disease). The Committee considered the benefits of triple combination therapy in terms of reductions in systolic and diastolic blood pressure and some evidence of improved adherence and persistence compared with free equivalent combination therapy. The Committee considered that the addition of the triple fixed-dose combinations is part of an overall strategy aimed at: meeting the different needs of both patients and health systems in addressing hypertension; ensuring patients can choose based on preference; and standardizing supply, procurement and training. Adverse effects are generally mild and manageable, and consistent with the known adverse-event profiles of the components. Cost comparisons of fixed-dose combinations with the sum of the component monotherapies vary across settings and should be considered in national selection decisions. The Committee reiterated the importance of continued availability of single-agent antihypertensives.

Section 13: Dermatological medicines

Section 13.1 Antifungal medicines

The Expert Committee did not recommend the inclusion of ciclopirox hydroxypropyl chitosan nail hydrolacquer on the EML for the treatment of onychomycosis in adults because of the lack of compelling evidence of comparative benefits and safety versus oral or combined oral and topical antifungal treatments, and unknown cost–effectiveness.

Section 13.4 Medicines affecting skin differentiation and proliferation

The Expert Committee considered that the inclusion of effective and safe biologics for psoriasis on the EML would address an important public health need and support global advocacy efforts to reduce the global burden of psoriasis, especially in low and middle-income countries. The Committee acknowledged that a large number of biologic disease-modifying medicines for psoriasis are available and that there was a need to prioritize the most effective, tolerable and affordable options.

The Expert Committee recommended the inclusion of adalimumab and ustekinumab on the complementary list of the EML and EMLc for the treatment of adults and children with moderate-to-severe psoriasis, based on evidence of favourable efficacy and safety, as second-line treatment alternatives. This listing complements the non-biologic therapies used in first-line treatment of psoriasis currently listed on the Model Lists (e.g. topical corticosteroids, systemic methotrexate).

The Committee considered that adalimumab and other tumour necrosis factor alpha inhibitors could be considered therapeutic alternatives to each other in most clinical scenarios and that including multiple within-class alternatives on the Model Lists could support greater competition to lower prices. The Committee therefore recommended adalimumab be listed with a square box as the class representative with certolizumab pegol, etanercept and infliximab as specified therapeutic alternatives.

The Committee recommended the inclusion of ustekinumab in addition to adalimumab because of some advantages ustekinumab has over adalimumab and other tumour necrosis factor alpha inhibitors. When considering the administration schedule, adalimumab is administered every 2 weeks while ustekinumab is administered every 12 weeks. Less frequent injections are more convenient, with reduced disruption to daily life for patients and reduced burden and costs for health systems. Ustekinumab is preferred to adalimumab in patients with heart disease and in settings where tuberculosis is endemic as this medicine is associated with a lower risk of tuberculosis reactivation. While ustekinumab is currently more highly priced than adalimumab, biosimilars are becoming increasingly available. For ustekinumab, the Committee did not recommend listing with a square box. The Committee acknowledged the data supporting the similar or better effectiveness of other monoclonal antibodies targeting IL-12 and IL-23 (e.g. guselkumab, risankizumab and tildrakizumab) but considered the alternatives had less supportive evidence, biosimilars were not yet available and no information existed on their costs in most jurisdictions which were assumed to be higher than ustekinumab.

Quality-assured biosimilars are recommended as therapeutic alternatives of both adalimumab (and therapeutic alternatives) and ustekinumab.

Section 13.6 Moisturizers

The Expert Committee recommended the inclusion of urea- and glycerol-based moisturizing creams on the EML and EMLc for the treatment of atopic dermatitis based on evidence of benefit, acceptable safety and public health need. Recommended formulations are creams containing 5% urea and creams containing 15% to 20% glycerol with regulatory approval as emollients.

Section 13.7 Sunscreens, broad spectrum

The Expert Committee recommended the inclusion of therapeutic broad-spectrum topical sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism. The Committee recognized the higher susceptibility to the harmful effects of ultraviolet (UV) radiation, including (but not limited to) non-melanoma skin cancer, among people with albinism and the therapeutic need for effective and safe sun protection products in this population. Therapeutic broad-spectrum sunscreens should contain proven active ingredients in appropriate amounts to absorb or filter UVA and UVB radiation and have a high sun protection factor. The Committee was not able to recommend specific formulations for listing at this time. The Committee considered that listing sunscreens, even without a preferred formulation, was important to stimulate greater investment in research to compare the various formulations available and identify those associated with a better profile. The Committee invited the submission of proposals outlining optimal formulation specifications for future consideration by the Expert Committee.

Section 15: Antiseptics and disinfectants

The Expert Committee recommended that an explicit listing for hypochlorous acid solution as an environmental disinfectant, separate from its general inclusion as a chlorine-based compound, be included on the EML and EMLc to aid differentiation between hypochlorite and hypochlorous acid products.

The Expert Committee did not recommend the inclusion of hypochlorous acid solution for topical use in antisepsis and wound care because the application did not provide an updated comprehensive review of clinical studies to inform the decision-making, as was the request of the Expert Committee in 2021. As was the case in 2021, the evidence in the application supporting topical use of hypochlorous acid solution in antisepsis and wound care was inconclusive.

Section 18: Medicines for endocrine disorders

Section 18.1 Adrenal hormones and synthetic substitutes

The Expert Committee recommended the inclusion of prednisolone 1 mg tablets on the core list of the EML and EMLc for treatment of adults and children with adrenal insufficiency based on evidence of an acceptable balance of benefits and harms and potential better affordability in some settings than currently listed hydrocortisone. Listing is recommended for prednisolone with a square box, specifying prednisone as a therapeutic alternative.

Section 18.5.1 Insulins

The Expert Committee recommended the inclusion of rapid-acting insulin analogues (insulin lispro, insulin aspart and insulin glulisine, and their quality-assured biosimilars as therapeutic alternatives) on the core list of the EML and EMLc for the treatment of people with type 1 and type 2 diabetes, and people with gestational diabetes. The Committee considered that the available evidence indicates generally comparable efficacy and safety between rapid-acting insulin analogues and regular human insulin. The Committee noted that some studies provide evidence of higher patient satisfaction scores with rapid-acting insulin analogues, and others suggest that rapid-acting insulin analogues may be associated with lower rates of complications, with medicine costs offset by reduced demand for high-cost treatments and health services for complications, particularly in type 1 diabetes. However, the Committee considered these arguments for including rapid-acting insulin analogues in the Model Lists to be tenuous. The Committee recognized that rapid-acting insulin analogues may be more expensive than regular human insulin and may be less affordable in some resource-limited settings. However, in other settings, the prices of rapid-acting insulin analogues do not exceed the price of regular human insulin. The Committee's reason for recommending listing of rapid-acting insulin analogues is to support access, recognizing the progressive withdrawal of regular human insulin from markets, and to signal to countries the need for multipronged policy, pricing and procurement strategies to strengthen affordable access. The inclusion of rapid-acting insulin analogues also enlarges the number of insulin products on the Model Lists and complements the listing of long-acting insulin analogues for use in basal-bolus regimens. This is also consistent with the listings for short- and intermediate-acting human insulins. Larger insulin markets could help stabilize prices, secure supply chains of quality-assured products and mitigate the risks of shortages. Countries in which insulin prices are excessive should consider strengthening the regulatory framework and implementing or maintaining price control or reference pricing mechanisms. The outcomes of price controls and reference pricing for essential medicines should be closely monitored as these policies can potentially have unintended consequences. The Committee emphasized the importance of commitment and action from WHO, Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally.

The Expert Committee also recommended the inclusion of 10 mL vial formulations of long-acting insulin analogues, in addition to the currently listed 3 mL prefilled pen and cartridge formulations.

Section 18.5.2 Hypoglycaemic agents

The Expert Committee recommended the inclusion of glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, dulaglutide and liraglutide) and GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists (tirzepatide) on the core list of the EML as add-on glucose-lowering therapy for adults with type 2 diabetes and with: (i) established cardiovascular disease or chronic kidney disease; and (ii) obesity (body mass index (BMI) $\geq 30 kg/m^2$) which has a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Listing is recommended for semaglutide with a square box, with dulaglutide, liraglutide and tirzepatide as specified therapeutic alternatives.

The Expert Committee did not recommend the inclusion of GLP-1 and GLP-1/GIP dual agonists on the EML for the treatment of people with obesity without the above-mentioned comorbidities (type 2 diabetes and established cardiovascular disease or chronic kidney disease) because of limited and less mature evidence of benefit for cardiovascular outcomes and mortality in this population and lack of data on long-term safety.

The Expert Committee considered two separate applications: one for the treatment of adults with type 2 diabetes and established or at high-risk of cardiovascular disease and one for the treatment of adults with obesity.

While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms in the two conditions and understand the implications of coverage for the two cohorts of patients at global, regional and national levels. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for the inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

The Committee recognized that diabetes and obesity are two major global health challenges, with both conditions reaching epidemic proportions in different populations and regions. According to the Global Burden of Disease Study, more than 500 million people worldwide were living with diabetes in 2021, a number projected to exceed 1.3 billion by 2050, reflecting large increases in all age groups, sexes and countries regardless of income level. Simultaneously, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affects more than 2 billion people. Increase in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are important contributors to mortality and morbidity and are responsible for significant disability-adjusted life years and straining health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with diabetes or obesity alone.

The Committee noted the evidence from multiple large-scale randomized controlled trials and systematic reviews demonstrating the efficacy of GLP-1 receptor agonists and GLP-1/GIP dual agonists compared to placebo in people with diabetes in improving glycaemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), reducing the risk of end-stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit is possible across all patients irrespective of their risk of cardiovascular diseases, the cohort of patients with type 2 diabetes with known cardiovascular or chronic kidney disease is a high-risk subgroup that is likely to experience the most relevant benefit, with a 10-

fold decreased risk of premature death compared to the cohort of patients at low risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify the patients who should be prioritized on the introduction of these medicines at the country level.

The Committee noted the evidence from a large systematic review demonstrating the efficacy GLP-1 receptor agonists and GLP-1/GIP dual agonists (particularly subcutaneous semaglutide and tirzepatide) compared with lifestyle modification alone in people with obesity for achieving clinically meaningful weight loss and improving quality of life. However, the Committee agreed that evidence for benefits in cardiovascular outcomes and mortality in people with obesity without diabetes is currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events among people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence with respect to mortality outcomes was still at an early stage and limited.

Overall, the Committee considered that the magnitude of benefits and certainty of evidence were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee placed greater value compared to outcomes of glycaemic control and weight loss.

Considering the population of people with type 2 diabetes, the Committee identified patients with established comorbid cardiovascular or chronic kidney disease as being the cohort for whom the net benefit of treatment was the greatest. The Committee then decided to include comorbid obesity (BMI $\geq 30\,kg/m^2$) as an additional eligibility criterion, thereby establishing a defined high-risk cohort of people for whom these medicines are listed as essential. The Committee considered the following reasons supported a triple target population: (i) obesity is a condition that can negatively affect both the mental and physical health of people with diabetes, stalling or worsening their health status; (ii) certain molecules within the pharmacological classes of GLP-1 receptor agonists and GLP-1/GIP dual agonists have an important effect on body weight, being associated with major weight reductions far exceeding the weight reductions associated with other hypoglycaemic agents on the EML (e.g. sodium-glucose cotransporter 2 inhibitors); and (iii) there is a need to highlight the importance of obesity as a public health priority – one that requires effective treatment and commitment at both scientific and policy levels.

The Committee noted that all proposed GLP-1 (semaglutide, liraglutide and dulaglutide) and GLP-1/GIP dual agonists (tirzepatide) were associated with important cardiovascular benefits in patients with type 2 diabetes. However, the Committee noted that there were important differences between these medicines for weight loss, with semaglutide and tirzepatide being associated with greater body weight reductions compared with the other molecules. The Committee noted that availability and use of semaglutide and tirzepatide were constrained by a price that currently limits their use to only well-resourced health-care systems.

The Committee acknowledged the current high price of these medicines and noted reported cost–effectiveness ratios that exceeded willingness-to-pay thresholds in many settings, particularly when used in low-risk patients. The Committee also noted the recent or upcoming patent expiry

for liraglutide and semaglutide, which will introduce the possibility for entry of generics, increased competition and lower prices. The Expert Committee believed that significant price reductions could be achieved with generic entry and competition, given the size and ubiquity of the market for these medicines. The Committee noted that when a large eligible patient population exists, robust generic competition has consistently proven to be more reliable at sustainably reducing prices than other price-reduction mechanisms. The Committee's decision to recommend a square box listing for semaglutide, with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives, aims to foster competition among available alternatives. The Committee hoped that having multiple EML-listed options would serve to facilitate the rapid introduction of prequalified generic formulations and would support countries in negotiating lower medicine prices and selecting the product that is the best value option.

The Expert Committee recommended listing of GLP-1 and GLP-1/GIP agonists in the core list to emphasize the importance of these medicines being available in the primary care setting. Type 2 diabetes and its complications, including obesity, are managed primarily in primary care. Delaying access by requiring hospital referral can reduce benefits associated with early intervention, add costs and limit availability in rural areas or underserved communities.

In recognition of the financial implications of including GLP-1 receptor agonists and GLP-1/GIP dual agonists in national health systems at their current prices, particularly in resource-limited settings, the Committee emphasized the importance of targeting use in the first instance to patients in whom the greatest value health benefit can be realized. The Committee also recommended that WHO continue to monitor the evolving landscape of this class of medicines, including benefits associated with use in people with obesity, potential long-term toxicities and approval of oral formulations. The Committee also recommended that WHO work on existing approaches for managing prices and evaluate alternative strategies to improve affordability and access to reduce the global burden of diabetes.

Section 19: Immunologicals

Section 19.3 Vaccines

The Expert Committee endorsed the inclusion of vaccines for Ebola and mpox on the core list of the EML and EMLc, vaccines for hepatitis E and respiratory syncytial virus on the core list of the EML, and vaccines for malaria on the core list of the EMLc, in line with recommendations of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization and corresponding WHO vaccine position papers.

Section 22: Medicines for reproductive health and perinatal care

Section 22.3 Uterotonics

The Expert Committee accepted the rationale presented in the application and endorsed the proposed changes to Section 22.3 of the Model Lists, as summarized in Table 3.

The Expert Committee also noted the advice of the decision by WHO to remove the boxed text associated with the listing for mifepristone and misoprostol.

Section 24: Medicines for mental and behavioural disorders

The Expert Committee did not recommend the inclusion of methylphenidate on the EML and EMLc for the treatment of children and adolescents with attention-deficit hyperactivity disorder (ADHD) because of limitations in the available evidence on the benefits and safety of long-term use, which reduced confidence in the estimates of prolonged beneficial effect.

The Committee acknowledged that methylphenidate is widely recommended and used in many countries as the standard of care for children and adolescents with ADHD and has wide regulatory approval and market availability. Furthermore, it is already included in the national essential medicines lists of some countries. The Committee noted there were currently no medicines for ADHD on the Model Lists.

The Committee recalled the recommendation of the 2021 Expert Committee to not include methylphenidate on the Model Lists because of persistent uncertainty about the benefit-to-harm ratio of the long-term use of this medicine. The 2021 Committee also recommended that any future consideration of methylphenidate should address: evidence of the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings.

The 2025 Expert Committee appreciated the efforts of the applicants of the current application in presenting evidence and information to address the 2021 Committee's concerns and the gaps in the evidence previously proposed for evaluation.

In consideration of the evidence presented in the current application for longer-term efficacy and safety of methylphenidate, the Committee noted that randomized controlled trials evaluating long-term treatment (> 6 months) were few and all had some methodological limitations. Selected pharmacoepidemiologic studies presented some real-world evidence of benefit in functional outcomes and reductions in all-cause mortality and unintentional injuries associated with long-term use of methylphenidate. However, these studies also had intrinsic methodological limitations. In particular, the Committee noted the findings of the 1999 Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA study), in which ADHD treatment with stimulant medication (not limited only to methylphenidate) was associated with greater improvements in ADHD symptoms when compared with behavioural management over a period of 14 months, as rated by parents, teachers or independent investigators. Stimulant treatment was not associated with an increase in serious adverse events. The Committee noted evidence identified during the review process from follow-up analyses of the MTA study which showed that the magnitude of benefit of stimulant treatment compared with behavioural management seen at 14 months reduced over time (after 2 years, 3 years, and into adulthood). The Committee noted that at longer follow-up the advantage associated with methylphenidate in symptom control was not retained when compared with other strategies, including behavioural therapy alone or community care. The Committee was unable to discern if the loss in sustained benefits was due to tolerance, less adherence, cross-over between different strategies, and if the change in effectiveness

was associated with characteristics of the children and adolescents or of the syndrome, such as baseline severity. Regarding long-term safety, the Committee noted mixed evidence of a potential association between methylphenidate use and effects on growth (height and weight) and the potential for adverse cardiovascular effects.

The Committee considered the conditional recommendation in the 2023 WHO mhGAP guidelines, based on low certainty of evidence, that methylphenidate may be considered for use in children (from 6 years) and adolescents with ADHD under clearly specified circumstances. The Committee considered that the mhGAP guidelines provide an important framework for supporting and increasing health system capacity to ensure the appropriate use of methylphenidate in children and adolescents. The Committee noted that the guidelines highlight, among other things: the limited evidence of efficacy and tolerability of methylphenidate beyond 12 weeks of treatment; that specialist reassessment of the patient's ADHD management plan should occur at least once a year; and the need for methylphenidate treatment to be offered only in the context of a comprehensive management plan. The Committee expressed concern about the current capacity of some health systems to ensure appropriate diagnosis, treatment (both pharmacological and non-pharmacological) and management of ADHD, particularly in low- and middle-income settings where reported rates of mental health workers for children and adolescents are low and among whom specialist psychiatrists are few.

Section 24.1 Medicines used in psychotic disorders

The Expert Committee recommended the inclusion of aripiprazole once-monthly long-acting injection on the core list of the EML for the treatment of adults with schizophrenia based on acceptable evidence for similar efficacy and a potentially lower risk of metabolic adverse effects compared with other long-acting injectable antipsychotics currently included on the EML (i.e. paliperidone, risperidone). Listing is recommended for aripiprazole as a therapeutic alternative under the square box listing for paliperidone once-monthly long-acting injection.

Section 24.2 Medicines used in mood disorders

The Expert Committee did not recommend the inclusion of brexpiprazole on the EML for adjunctive treatment of major depressive disorder in adults based on evidence from short-term studies showing only modest incremental benefits compared with placebo and noting that other atypical antipsychotics and lithium had similar or superior gains. The Committee noted that the EML does not currently include any medicines for adjunctive treatment of major depressive disorder and advised that any future application should present a comprehensive evaluation of the evidence for all relevant treatment options for this indication, in preference to an application that focuses on a single medicine.

Section 24.5.2 Medicines for nicotine use disorders

The Expert Committee recommended the inclusion of cytisine (International Nonproprietary Name: cytisinicline) on the core list of the EML as an aid to stopping smoking and tobacco use, based on a favourable balance of benefits and harms, in an area of great public health need. The

Committee considered that the availability of different smoking cessation treatments provides valuable options and choice for patients and clinicians, could facilitate market competition, reduces costs and improves access to effective smoking and tobacco cessation treatments for national health systems.

Section 27: Vitamins and minerals

The Expert Committee recommended deletion of iodine capsules from the EML and EMLc for prevention and treatment of iodine deficiency, noting that the formulation is no longer marketed or used in iodine supplementation programmes in any countries.

Other matters considered by the Expert Committee

Age-appropriateness of formulations of essential medicines for children

In consideration of the review of the age-appropriateness of formulations of medicines on the EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the review. Corresponding changes to the EML were made for consistency, as appropriate. All changes are reported in Tables 1, 2 and 3. The Committee also noted the proposals made in the review for consideration by the Global Accelerator for Paediatric Formulations (GAP-f) network, where gaps in the availability of age-appropriate formulations of essential medicines for children exist.

Revision of AWaRe (Access, Watch, Reserve) definitions, classification and reclassification of antibiotics

The Expert Committee considered the applications proposing:

- a revision of the current AWaRe definitions for AWaRe classification and criteria for inclusion of AWaRe antibiotics on the Model Lists;
- classification of antibiotics not currently included in the WHO AWaRe classification database; and
- reclassification of cefoperazone + sulbactam from "not recommended" to the AWaRe Watch group.

The Committee acknowledged the growing importance and adoption of AWaRe as a global tool for antibiotic selection, stewardship, surveillance and policy development, and its strong relationship with the WHO Model Lists of Essential Medicines.

The Committee noted that the definitions of AWaRe groups were developed between 2017 and 2019, reflecting the evaluation of antibiotics that were recommended for inclusion in the Model Lists. The Committee accepted that the current definition of Reserve antibiotics – intended for use as so-called last resort options in life-threatening infections due to multidrug-resistant bacteria should adapt to the needs of changing public health policies and priorities. The Committee

considered that several aspects of the current definition could evolve, expand or be modified. These include expanding guidance on the level of evidence required to demonstrate so-called proven activity against WHO priority pathogens, clarifying whether the relationship between the Reserve definition and the WHO Bacterial Priority Pathogens List is binding, and developing standardized definitions for multidrug resistance. The Committee also recognized the limited clinical evidence available to guide empiric use of Reserve antibiotics, particularly in low-resource settings. The Committee determined that there was also a need to consider additional dimensions in the selection of Reserve antibiotics for the Model Lists, including innovation criteria, access challenges and strategies to increase access, and the role of real-world evidence.

The Committee noted a growing debate about how the definition of Reserve antibiotics should evolve. The Committee also noted the comments of the WHO Technical Advisory Group on AWaRe (TAG-AWaRe) calling for a comprehensive reassessment of all AWaRe categories, with the establishment of clear criteria for AWaRe classification groups. This reassessment should consider a number of dimensions, including efficacy, safety, impact on the emergence and spread of resistance, and impact on the microbiome. The reassessment should also link to other WHO products, including (but not limited to) the Bacterial Priority Pathogens Lists, the Medically Important Antimicrobial List and the report of antibacterial agents in clinical and preclinical development.

Given the complexity of refining definitions for all AWaRe categories, the Expert Committee requested the WHO Secretariat to coordinate a structured, inclusive review process, involving broad stakeholder consultation and a review of available evidence, with the aim of strengthening the AWaRe framework as a cornerstone of global antimicrobial stewardship and access policy. The recommendations of this review should be submitted for consideration by the 2027 Expert Committee. Therefore, the Committee did not recommend any changes to the current AWaRe definitions.

Consequently, until such time as the definitions of AWaRe categories are revised, the Committee did not recommend any change to the current classification of cefoperazone + sulbactam. The Committee also noted that numerous other beta-lactam + beta-lactamase inhibitor combinations are also currently classified as "not recommended" and considered that reclassifying only one such combination at this time would introduce inconsistency.

In consideration of the request to classify antibiotics not currently included in the AWaRe classification, the Expert Committee accepted the rationale presented in the application and recommended the antibiotics identified in the application be classified as Access, Watch, Reserve, not recommended, or remain unclassified, as proposed (Table 5).

Commemoration of the 50th anniversary of the WHO Model List of Essential Medicines in 2027

The Expert Committee noted the report of the meeting on revising the procedures for updating the Model Lists of Essential Medicines, convened by WHO at its headquarters in Geneva in November 2023 (2). The Committee welcomed and endorsed all following key messages that emerged during the meeting.

- The importance of strengthening alignment and integration of the EML with related WHO guidelines and products to reduce redundant efforts, mitigate contradicting messages and facilitate coordinated evidence-based policy-making. This involves harmonizing procedures and identifying and then addressing situations of discordance.
- The importance of improving dissemination strategies related to the selection of medicines. This includes providing information not only about medicines that are listed but also those that have not been recommended for listing. Rejections can be informative, as medicines rejected for addition to the EML might have drawbacks in terms of efficacy and safety, equity, feasibility, cost–effectiveness or access, with implications for national EMLs.
- The value of developing a structured process for prioritizing disease areas and medicines for EML applications to ensure an orderly, proactive approach, particularly in overlooked disease areas. Coordinated applications could be developed by utilizing partnerships with professional societies.
- The need to improve the extent and quality of information on price, cost and cost–effectiveness considered in EML selection. This requires, among other strategies, incorporating data on pricing of medicines (including generics and biosimilars and their availability) and the financial impact on patients in terms of out-of-pocket expenditure.
- Modernizing and investigating resources that can aid the selection process. Electronic support systems such as digital submission forms, artificial intelligence to increase efficiency and precision in administrative processes, and more human resources to enable the Secretariat to improve the quality of the selection process were proposed.
- The need to ensure sustained progress in improving access. This requires tackling systemic barriers beyond medicine selection. It is crucial to study the accessibility of certain medicines once they have been listed in the EMLs to evaluate if their essential medicine status contributes to improved access, and understand the role of pricing opacity, production barriers limiting generic availability, and inconsistent supply and delivery and inappropriate marketing influences.

The Committee considered that many of these recommendations relate directly to activities that address WHO's mandate to advise Member States on the selection and procurement of essential medicines that offer the best value health outcomes.

The Committee highlighted that the 50th anniversary of the WHO EML presents a valuable opportunity for Member States to actively participate in commemorating the EML and recognizing its impact on national policies and essential medicines lists. The Committee considered that updates of national lists in 2027 should be a main activity of the commemorations. These updates should not be aimed solely at adding new medicines to national lists but should also aim to achieve greater alignment between national EMLs and national reimbursement lists, with transparent reporting of what is made available as part of universal health coverage policies. Consideration should be given to strengthening national EMLs by developing lists that specify the indications for which medicines are considered essential.

Other important elements of the commemoration updates include:

- transparent inclusion of medicines and age-appropriate formulations for children – disappointingly, less than 15% of countries prioritize medicines and formulations for children in their national lists (*3*);
- clear reporting of priority formulations to guide supply and procurement and to limit fragmentation;
- optimizing interpretation and implementation of guidance on therapeutic alternative (square box listings) in the EMLs.

The 50th anniversary of the WHO EML is an important opportunity for Member States to reaffirm the fundamental right to access essential medicines. By participating in the celebration, updating national tools, promoting public engagement and strengthening policies, countries can help ensure that essential medicines remain a living, evolving and effective instrument for health equity.

Improving the quality of EML applications

The Expert Committee noted a general improvement in the quality of applications under evaluation at the current meeting, although considerable variability remained between applications.

The Committee expressed appreciation for the open and participatory nature of the application process, where applications may be submitted by individuals, institutions, public and private sector organizations and other stakeholders. However, in many cases, applications are developed on an ad hoc and voluntary basis and sometimes lack sufficient scientific rigour (e.g. management of inherent biases), fail to present benefits across different patient subgroups, and often lack comprehensive analyses of feasibility, cost–effectiveness and budget impact in different settings. The Committee considered that applications for the EML would benefit from following a process similar to that of WHO's guideline development processes, which should also facilitate alignment of the recommendations in these two WHO tools, and orient selection and appropriate use of medicines recommended by WHO.

The Committee commended two applications for exemplifying a high standard of scrutiny and comprehensive evaluation of multiple therapeutic options within specific disease areas: the 2023 application proposing essential medicines for the treatment of multiple sclerosis (*4*) and the 2025 application proposing PD-1/PD-L1 immune checkpoint inhibitors for various cancers (*5*). These applications were the result of a coordinated effort by multiple entities including academic groups, scientific societies, methodology support teams and close collaboration with the EML Secretariat. Notable strengths were the use of a comprehensive, disease-focused strategy with clear prioritization criteria, rather than a narrower focus on individual medicines, and the systematic use of GRADE Evidence to Decision (EtD) tables to summarize the findings.

The Committee highlighted that the adoption of guiding decision-making frameworks to suit EML requirements, particularly the capacity of these frameworks to clarify how the magnitude of benefits varied across different therapeutic options and patient subgroups, greatly facilitated the Committee's decision-making. The Committee appreciated the efforts of the WHO Secretariat to

better align the EML selection process with established guideline development tools, such as the GRADE EtD framework, to enhance transparency and assessment of the quality of evidence.

The Committee advised that the incorporation of EtD tables in EML applications going forward was desirable. However, the Committee recognized that it would take time for a methodological and reporting approach to become an integral part of the application process, and that it may preclude or discourage applicants without the necessary expertise or capacity to develop EtD tables from participating in the EML process, an outcome that should be avoided. The Committee considered that a possible way to mitigate this risk would be to develop a structured process for setting priorities for EML applications where applicant participation can be encouraged and supported by public health partners.

Finally, the Committee observed that the number of applications for newer, patented, highly priced medicines has grown considerably over time. The Committee considered that the voluntary nature of the current application process has the potential to give rise to gaps in selection and coverage of older (but no less important) medicines for which there may be less commercial interest. The Committee recommended WHO develop a strategy guided by priority needs to complement the existing application process to ensure applications for essential medicine candidates are submitted, regardless of their stage in the medicine life cycle.

Table 1

Recommended changes on the 2025 EML

EML – New medicines added	
Medicine	**Indication**
Baclofen	Spasticity in cerebral palsy
Blinatumomab	CD-19 positive, B-lineage acute lymphoblastic leukaemia
Coagulation factor VIII (recombinant)	Haemophilia A
Coagulation factor IX (recombinant)	Haemophilia B
Cytisine	Smoking and tobacco cessation
Ebola vaccine	Ebola virus disease
Elexacaftor + tezacaftor + ivacaftor	Cystic fibrosis
Emicizumab	Haemophilia A
Glycerol (cream, 15%–20%)	Atopic dermatitis
Hepatitis E vaccine	Hepatitis E
Insulin, analogue rapid-acting	Type 1 and type 2 diabetes
Ivacaftor	Cystic fibrosis
Mpox vaccine	Mpox
Pembrolizumab (with atezolizumab and cemiplimab as therapeutic alternatives)	Metastatic cervical cancer, metastatic colorectal cancer, metastatic non-small cell lung cancer
Perindopril + amlodipine + indapamide (with within-class medicines as therapeutic alternatives)	Hypertension
Respiratory syncytial virus vaccine	Maternal RSV vaccination
Semaglutide (with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives)	Type 2 diabetes in people with established cardiovascular or chronic kidney disease, and with obesity
Sunscreen, broad-spectrum	Prevention of skin cancer in persons with albinism
Ustekinumab	Moderate-to-severe psoriasis
Valsartan + amlodipine + hydrochlorothiazide (with within-class medicines as therapeutic alternatives)	Hypertension

Table 1 *continued*

EML – New indications	
Medicine	**Indication**
Adalimumab (with certolizumab pegol, etanercept and infliximab as therapeutic alternatives)	Moderate-to-severe psoriasis
Fexinidazole	Human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* infection
Ibuprofen	Acute migraine
Prednisolone	Adrenal insufficiency, cluster headache
Sumatriptan (subcutaneous formulation)	Cluster headache
Urea (cream 5%)	Atopic dermatitis
Verapamil	Cluster headache
EML – New formulation/strength	
Medicine	**Formulation/strength**
Acetylsalicylic acid	Suppository: 300 mg Tablet (dispersible): 75 mg, 300 mg, 500 mg.
Aciclovir	Solution for infusion: 25 mg/mL (as sodium) in vial
Aripiprazole	Injection (prolonged-release): 300 mg, 400 mg as powder and solvent for suspension (as therapeutic alternative to paliperidone prolonged-release injection)
Artemether	Oily injection: 20 mg/mL, 40 mg/mL in 1 mL ampoule
Artesunate	Powder for injection: 30 mg, 60 mg, 120 mg in vial
Artesunate – sulfadoxine + pyrimethamine	Co-packaged scored tablets: artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1] (Section 6.5.3.1)
Budesonide	Powder for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in dry powder inhaler Suspension for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in pressurized metered-dose inhaler.
Charcoal, activated	Granules for oral suspension: 50 g

Table 1 *continued*

EML – New formulation/strength	
Medicine	**Formulation/strength**
Dihydroartemisinin + piperaquine	Tablet: 60 mg + 480 mg (phosphate), 80 mg + 640 mg (phosphate)
Dimercaprol	Injection in oil: 100 mg/mL in 3 mL ampoule
Insulin, analogue long-acting	Injection solution: 100 IU/mL in 10 mL vial
Mesna	Injection: 100 mg/mL in 2 mL ampoule
Midazolam	Solution for oromucosal administration: 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL 3 mL prefilled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL prefilled syringe (Section 2.3)
Omeprazole	Powder for oral liquid: 1 mg/mL, 4 mg/mL
Phytomenadione	Injection: 2 mg/0.2 mL, 10 mg/mL in ampoule (mixed micelle solution). Tablet: 5 mg
Pyridostigmine	Injection: 5 mg/mL (bromide) in ampoule or vial
Retinol	Injection (water-miscible): 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial
Salbutamol	Injection 500 micrograms/mL in 1 mL, 5 mL ampoule Solution for inhalation: 100 micrograms (as sulfate) per actuation in pressurized metered dose inhaler; 2.5 mg/2.5 mL, 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multidose bottle for use in nebulizers
Warfarin	Tablet (scored): 3 mg (sodium)
EML – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Acetylcysteine	Oral liquid: 10%, 20%
Acetylsalicylic acid	Suppository: 50 mg
Amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
Artemether	Oily injection: 80 mg/mL

Table 1 *continued*

EML – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Artesunate	Injection: ampoules containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution Rectal dosage form: 50 mg, 200 mg capsules Tablet: 50 mg
Budesonide	Inhalation (aerosol): 100 micrograms per dose, 200 micrograms per dose
Charcoal, activated	Powder
Chloroquine	Tablet: 100 mg (as phosphate or sulfate)
Coagulation factor IX complex (plasma-derived)	Removed as a therapeutic alternative to coagulation factor IX (plasma-derived)
Cryoprecipitate (pathogen-reduced, non-pathogen reduced)	Removed for indications of haemophilia A, von Willebrand disease
Halothane	Inhalational anaesthetic
Iodine	Capsule: 190 mg Iodized oil: 0.5 mL (240 mg iodine) in ampoule (oral or injectable), 0.57 mL (308 mg iodine) in dispenser bottle
Mefloquine	Tablet: 250 mg (as hydrochloride) (Section 6.5.3.1)
Methimazole	Tablet: 20 mg
Omeprazole	Powder for oral liquid: 20 mg, 40 mg sachets
Phytomenadione	Tablet: 10 mg
Proguanil	Tablet: 100 mg (as hydrochloride)
Propranolol	Tablet: 20 mg (hydrochloride)
Pyridostigmine	Injection: 1 mg in 1 mL ampoule
Quinine	Tablet: 300 mg (sulfate) or 300 mg (bisulfate)
Retinol	Tablet (sugar-coated): 100 000 IU (as palmitate) Water-miscible injection: 100 000 IU (as palmitate) in 2 mL ampoule
Ribavirin	All listed formulations and strengths for viral haemorrhagic fevers

Table 1 *continued*

EML – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Salbutamol	Injection: 50 micrograms/mL (as sulfate) in 5 mL ampoule Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose
Sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg (Section 6.5.3.1) Tablet: 250 mg + 12.5 mg (Section 6.5.3.2)
Suxamethonium	Powder for injection: (chloride) in vial

Table 2
Recommended changes on the 2025 EMLc

EMLc – New medicines added	
Medicine	**Indication**
Abacavir + dolutegravir + lamivudine	HIV
Baclofen	Spasticity in cerebral palsy
Blinatumomab	CD-19 positive, B-lineage acute lymphoblastic leukaemia
Coagulation factor VIII (recombinant)	Haemophilia A
Coagulation factor IX (recombinant)	Haemophilia B
Ebola vaccine	Ebola virus disease
Elexacaftor + tezacaftor + ivacaftor	Cystic fibrosis
Emicizumab	Haemophilia A
Glycerol (cream, 15%–20%)	Atopic dermatitis
Insulin, analogue rapid-acting	Type 1 and type 2 diabetes
Ivacaftor	Cystic fibrosis
Malaria vaccine	Malaria
Mpox vaccine	Mpox
Sunscreen, broad-spectrum	Prevention of skin cancer in persons with albinism
Ustekinumab	Moderate-to-severe psoriasis
EMLc – New indications	
Medicine	**Indication**
Adalimumab (with certolizumab pegol, etanercept and infliximab as therapeutic alternatives)	Moderate to severe psoriasis
Fexinidazole	Human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* infection
Prednisolone	Adrenal insufficiency, infantile spasm
Urea (cream 5%)	Atopic dermatitis

Table 2 *continued*

EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Acetylsalicylic acid	Suppository: 300 mg Tablet (dispersible): 75 mg, 300 mg, 500 mg.
Aciclovir	Solution for infusion: 25 mg/mL (as sodium) in vial
Allopurinol	Powder for injection: 500 mg (as sodium)
Amitriptyline	Oral liquid: 25 mg/5 mL (Section 2.3)
Amodiaquine – sulfadoxine + pyrimethamine	Co-packaged dispersible tablets: amodiaquine 75 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 150 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]
Amoxicillin + clavulanic acid	Tablet (dispersible): 250 mg (as trihydrate) + 62.5 mg (as potassium salt) (Section 6.2.5)
Artemether	Oily injection: 20 mg/mL, 40 mg/mL in 1 mL ampoule
Artesunate	Powder for injection: 30 mg; 60 mg, 120 mg in vial
Artesunate – sulfadoxine + pyrimethamine	Co-packaged scored tablets: artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]
Atropine	Injection: 400 micrograms/mL (sulfate) in 1 mL ampoule or vial
Budesonide	Nasal spray: 30 micrograms per actuation, 64 micrograms per actuation Powder for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in dry powder inhaler Suspension for inhalation: 100 micrograms per actuation, 200 micrograms per actuation in pressurized metered-dose inhaler.
Charcoal, activated	Granules for oral suspension: 50 g
Desmopressin	Nasal spray: 150 micrograms (acetate) per actuation
Dexamethasone	Oral liquid: 0.5 mg/5 mL (as sodium phosphate) Tablet: 0.5 mg; 0.75 mg; 1.5 mg; 5 mg (as dexamethasone base) (Sections 2.3, 3, 8.2.4 and 17.2)

Table 2 *continued*

EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Diazepam	Tablet (scored): 2 mg (Section 2.3)
Dihydroartemisinin + piperaquine	Tablet: 60 mg + 480 mg (phosphate), 80 mg + 640 mg (phosphate) Tablet (dispersible): 20 mg + 160 mg (phosphate), 40 mg + 320 mg (phosphate)
Dimercaprol	Injection in oil: 100 mg/mL in 3 mL ampoule
Docusate sodium	Oral liquid: 12.5 mg/5 mL
Ferrous salts	Oral liquid: equivalent to 9 mg/mL elemental iron
Fludrocortisone	Oral liquid: 100 micrograms/mL (acetate)
Folic acid	Oral liquid: 1 mg/mL
Hydrochlorothiazide	Solid oral dosage form: 12.5 mg
Hydrocortisone	Granules: 0.5 mg, 1 mg, 2 mg, 5 mg in capsule
Insulin, analogue long-acting	Injection solution: 100 IU/mL in 10 mL vial
Ketamine	Injection: 10 mg/mL (as hydrochloride) in vial
Lidocaine	Injection: 0.5% (hydrochloride)
Loratadine	Tablet (chewable): 5 mg, 10 mg
Mesna	Injection: 100 mg/mL in 2 mL ampoule
Methylprednisolone	Powder for injection: 125 mg (as sodium succinate) in vial
Midazolam	Solution for oromucosal administration: 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL , 2 mL prefilled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL prefilled syringe (Section 2.3)
Morphine	Injection: 1 mg/mL; 2 mg/mL (morphine hydrochloride or morphine sulfate) in 1 mL vial (Section 1.3, Section 2.2) Oral liquid: 5 mg/5 mL (morphine hydrochloride or morphine sulfate) (Section 2.2) Solid oral dosage form (slow-release): 5 mg (Section 2.2)
Omeprazole	Powder for oral liquid: 1 mg/mL, 4 mg/mL

Table 2 *continued*

EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Ondansetron	Injection: 2 mg/mL in 4 mL ampoule (as hydrochloride dihydrate) (Section 2.3, Section 17.2)
Oseltamivir	Powder for oral liquid: 6 mg/mL (as phosphate)
Phytomenadione	Injection, mixed micelle solution: 2 mg/0.2 mL; 10 mg/mL in ampoule Injection: 1 mg/0.5 mL Tablet: 5 mg
Propranolol	Tablet: 10 mg (hydrochloride)
Pyridostigmine	Injection: 5 mg/mL (bromide) in ampoule or vial
Pyridoxine	Tablet: 10 mg
Quinine	Solution for infusion: 60 mg/mL (hydrochloride) in 2 mL ampoule
Retinol	Injection (water-miscible): 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial
Rifapentine	Tablet (dispersible, scored): 150 mg
Salbutamol	Injection 500 micrograms/mL in 1 mL, 5 mL ampoule Solution for inhalation: 100 micrograms (as sulfate) per actuation in pressurized metered dose inhaler; 2.5 mg/2.5 mL, 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multi-dose bottle for use in nebulizers
Sofosbuvir	Granules: 200 mg in sachet
Sofosbuvir + velpatasvir	Granules: 150 mg + 37.5 mg; 200 mg + 50 mg in sachet
Spironolactone	Tablet 12.5 mg
Sulfadoxine + pyrimethamine	Tablet (dispersible): 250 mg + 12.5 mg
Thiamine	Injection: 50 mg/mL (hydrochloride) in ampoule or vial
Warfarin	Tablet (scored): 3 mg (sodium)
Xylometazoline	Nasal drops: 0.05%

Table 2 *continued*

EMLc – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Acetylcysteine	Oral liquid: 10%, 20%
Acetylsalicylic acid	Suppository: 50 mg
Amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
Aprepitant	Capsule: 80 mg, 125 mg, 165 mg
Artemether	Oily injection: 80 mg/mL
Artesunate	Injection: ampoules containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution Rectal dosage form: 50 mg, 200 mg capsules Tablet: 50 mg
Budesonide	Inhalation (aerosol): 100 micrograms per dose, 200 micrograms per dose Nasal spray: 100 micrograms per dose
Charcoal, activated	Powder
Chloroquine	Tablet: 100 mg (as phosphate or sulfate)
Coagulation factor IX complex (plasma-derived)	Removed as a therapeutic alternative to coagulation factor IX (plasma-derived)
Cryoprecipitate (pathogen-reduced, non-pathogen reduced)	Removed for indications of haemophilia A, von Willebrand disease
Desmopressin	Nasal spray: 10 micrograms (as acetate) per dose
Diazepam	Injection: 5 mg/mL (Section 2.3)
Docusate sodium	Capsule: 100 mg
Halothane	Inhalation
Iodine	Capsule 190 mg Iodized oil: 0.5 mL (240 mg iodine) in ampoule (oral or injectable), 0.57 mL (308 mg iodine) in dispenser bottle
Mefloquine	Tablet: 250 mg (as hydrochloride)
Methadone	Tablet: 10 mg (hydrochloride) Oral liquid: 10 mg/5 mL (hydrochloride) Concentrate for oral liquid: 10 mg/mL (hydrochloride)
Methimazole	Tablet: 20 mg

Table 2 *continued*

EMLc – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Methylprednisolone	Injection: 80 mg/mL (Section 8.2.4)
Midazolam	Tablet: 7.5 mg; 15 mg
Morphine	Granules (slow release; to mix with water): 200 mg (morphine sulfate) Tablet (slow release): 200 mg (morphine hydrochloride or morphine sulfate)
Neostigmine	Tablet: 15 mg (bromide)
Omeprazole	Powder for oral liquid: 20 mg, 40 mg sachets
Phytomenadione	Tablet: 10 mg
Proguanil	Tablet: 100 mg (as hydrochloride)
Propranolol	Tablet: 20 mg (hydrochloride)
Pyridostigmine	Injection: 1 mg in 1 mL ampoule
Quinine	Tablet: 300 mg (sulfate) or 300 mg (bisulfate)
Retinol	Tablet (sugar-coated): 100 000 IU (as palmitate) Water-miscible injection: 100 000 IU (as palmitate) in 2 mL ampoule
Ribavirin	All listed formulations and strengths for viral haemorrhagic fevers
Salbutamol	Injection: 50 micrograms/mL (as sulfate) in 5 mL ampoule Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose
Spironolactone	Oral liquid: 5 mg/5 mL, 10 mg/5 mL
Sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg (Section 6.5.3.1) Tablet: 250 mg + 12.5 mg (Section 6.5.3.2)
Suxamethonium	Powder for injection: (chloride) in vial

Table 3
Other changes on the 2025 EML and EMLc

Other changes to listings – EML and/or EMLc		
Acetic acid	Modify formulation description to better describe available dosage forms.	EMLc
Acetylsalicylic acid	Modify formulation description to include a strength range for tablets from 75 mg to 500 mg.	EMLc
Aciclovir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Arpraziquantel	Add arpraziquantel 150 mg dispersible tablets to the EMLc as a therapeutic alternative to praziquantel for treatment of schistosomiasis.	EMLc
Artemether + lumefantrine	Remove note.	EML & EMLc
Artesunate	Amend note.	EML & EMLc
Artesunate + amodiaquine	Remove note.	EML & EMLc
Artesunate + mefloquine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Artesunate + pyronaridine	Modify formulation descriptions to better describe available dosage forms. Remove note.	EML & EMLc
Atropine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Budesonide	Remove flunisolide as a therapeutic alternative.	EML & EMLc
Bupivacaine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Calcium gluconate	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Charcoal, activated	Add note stating "alternative formulations of activated charcoal may be used if granules are not available"	EML & EMLc
Chloroquine	Modify formulation descriptions to better describe available dosage forms. Transfer listing of chloroquine in malaria chemoprevention section to new subsection for malaria chemoprophylaxis in travellers.	EML & EMLc
Cyclizine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Daclatasvir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Daclatasvir + sofosbuvir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Dexamethasone	Modify formulation description to reflect amount of dexamethasone in terms of salt or base.	EML & EMLc
Dihydroartemisinin + piperaquine phosphate	Modify formulation descriptions to better describe available dosage forms. Remove note.	EML & EMLc
Diloxanide	Proposed for deletion in 2027.	EML & EMLc
Doxycycline	Transfer listings of doxycycline in malaria treatment and chemoprevention sections to new subsection for malaria chemoprophylaxis in travellers.	EML & EMLc
Eletriptan	Add eletriptan to the EML as a therapeutic alternative to sumatriptan for acute migraine.	EML
Ferrous salts	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Fomepizole	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Glucagon	Modify formulation description to better describe available dosage forms.	EML & EMLc
Heparin sodium	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Hydroxocobalamin	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Hypochlorous acid	Separate listing for hypochlorous acid solution as an environmental disinfectant	EML & EMLc
Insulin injection (soluble)	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc
Intermediate-acting insulin	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Intraperitoneal dialysis solution	Modify formulation description to better describe available dosage forms.	EML & EMLc
Iodine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Isoniazid	Modify formulation descriptions to better describe available dosage forms.	EMLc
Ketamine	Remove specification of vial size.	EML & EMLc
Lactulose	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Levetiracetam	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Lidocaine	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Lidocaine + epinephrine (adrenaline)	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Linezolid	Modify formulation descriptions to better describe available dosage forms.	EMLc
Long-acting insulin analogues	Modify formulation descriptions to better describe available dosage forms. Update medicine description to better differentiate between human and analogue insulins.	EML & EMLc
Lugol's solution	Modify formulation descriptions to better describe available dosage forms. Update medicine description to reflect active ingredients.	EML & EMLc
Mannitol	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Medicines for multidrug-resistant tuberculosis	Transfer from complementary to core list	EML & EMLc
Mefloquine	Transfer listings of mefloquine in malaria chemoprevention section to new subsection for malaria chemoprophylaxis in travellers.	EML & EMLc
Mesna	Add note to indicate injection solution may also be used for oral administration.	EML & EMLc
Methadone	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Metoclopramide	Modify formulation description to better describe available dosage forms. Remove note.	EML & EMLc
Midazolam	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Mifepristone – misoprostol	Transfer listing to the new subsection for medicines for medical abortion.	EML
Misoprostol	Transfer listing for the indication of management of incomplete abortion to the new subsection for medicines for medical abortion.	EML
Morphine	Modify formulation descriptions to better describe available dosage forms. Replace strength ranges for slow-release granules and solid oral dosage forms with specific strengths.	EML & EMLc
Moxidectin	Add moxidectin to the EML and EMLc as a therapeutic alternative to ivermectin for treatment of onchocerciasis and lymphatic filariasis	EML & EMLc
Naproxen	Add naproxen to the EML as a therapeutic alternative to ibuprofen for acute migraine.	EML
Nivolumab/ pembrolizumab	Reverse the current listing for malignant melanoma to make pembrolizumab the representative medicine and nivolumab a therapeutic alternative.	EML
Ondansetron	Modify formulation description to better describe available dosage forms.	EML & EMLc
Oral rehydration salts	Modify formulation description to better describe available dosage forms.	EML & EMLc
Oral rehydration salts – zinc sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc
Pancreatic enzymes	Modify formulation description to better describe available dosage forms.	EML & EMLc
Phenobarbital	Replace strength range for tablet formulation with specific strengths (15 mg, 30 mg, 60 mg, 100 mg)	EML & EMLc
Potassium iodide	Modify formulation description to better describe available dosage forms.	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Primaquine	Amend note.	EML & EMLc
Prostaglandin E1/ E2	Update medicine descriptions to reflect active ingredients by International Nonproprietary Names (alprostadil/dinoprostone).	EML & EMLc
Protamine sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc
Pyridostigmine	Modify formulation description to better describe available dosage forms.	EML & EMLc
Quinine	Modify formulation descriptions to better describe available dosage forms. Amend note.	EML & EMLc
Rasburicase	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Retinol	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Surfactant	Update medicine and formulation description to reflect active ingredients by International Nonproprietary Names (beractant, poractant alfa) and corresponding dosage forms.	EMLc
Valganciclovir	Modify formulation descriptions to better describe available dosage forms.	EML & EMLc
Warfarin	Modify formulation descriptions to better describe available dosage forms. Specify acenocoumarol as a therapeutic alternative.	EML & EMLc
Xylometazoline	Remove note.	EMLc
Zanubrutinib	Add zanubrutinib to the EML as a therapeutic alternative to ibrutinib for treatment of relapsed/ refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma.	EML
Zinc sulfate	Modify formulation description to better describe available dosage forms.	EML & EMLc

Table 3 *continued*

Changes to sections and sub-sections		
	2023	**2025**
Section 5	Medicines for diseases of the nervous system	Medicines for neurological disorders
Section 5.1	Antiseizure medicines	Medicines for central nervous system disorders 5.1.1 Antiseizure medicines 5.1.2 Medicines for multiple sclerosis 5.1.3 Medicines for parkinsonism 5.1.4 Medicines for cerebral palsy 5.1.5 Medicines for headache disorders 5.1.5.1 Medicines for acute migraine attacks 5.1.5.2 Medicines for migraine prophylaxis 5.1.5.3 Medicines for cluster headache 5.1.6 Medicines for central nervous system infections 5.1.6.1 Medicines for bacterial central nervous system infections 5.1.6.2 Medicines for viral central nervous system infections
Section 5.2	Medicines for multiple sclerosis	Medicines for peripheral nervous system disorders 5.2.1 Medicines for Guillain–Barre syndrome 5.2.2 Medicines for myasthenia gravis
Section 5.3	Medicines for parkinsonism	N/A
Section 6.5.3.3	N/A	Medicines for chemoprophylaxis in travellers
Section 7	Antimigraine medicines	Medicines for cystic fibrosis
Section 10.3	Other medicines for haemoglobinopathies	Medicines for haemoglobinopathies
Section 11	Blood products of human origin and plasma substitutes	Blood products, coagulation factors and plasma substitutes
Section 11.2	Plasma-derived medicines	Human immunoglobulins
Section 11.3	Plasma substitutes	Coagulation factors

Table 3 *continued*

Changes to sections and sub-sections		
	2023	**2025**
Section 11.4	N/A	Plasma substitutes
Section 13.6	N/A	Moisturizers
Section 13.7	N/A	Sunscreens, broad-spectrum
Section 18.5.2	Oral hypoglycaemic agents	Hypoglycaemic agents
Section 22.4	Antioxytocics (tocolytics)	Medicines for medical abortion
Section 22.5	Other medicines administered to the mother	Antioxytocics (tocolytics)
Section 22.6	Medicines administered to the neonate	Other medicines administered to the mother
Section 22.7	N/A	Medicines administered to the neonate

EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for Children; N/A: not applicable.

Table 4
Applications not recommended

New medicines/indications	
Addition of brexpiprazole for adjunctive treatment of major depressive disorder	EML
Addition of temozolomide for high grade glioma, Ewing sarcoma, neuroblastoma	EMLc
Addition of erythropoiesis-stimulating agents for the new indication of chemotherapy-induced anaemia	EML & EMLc
Addition of methylphenidate for treatment of attention deficit hyperactivity disorder	EML & EMLc
Addition of pembrolizumab for treatment of metastatic: endometrial cancer, gastric or gastro-oesophageal junction adenocarcinoma, head and neck squamous cell carcinoma, oesophageal squamous cell carcinoma, renal cell carcinoma, triple-negative breast cancer	EML
Addition of nivolumab and ipilimumab (as combination treatment) for treatment of metastatic: colorectal cancer, malignant melanoma, non-small cell lung cancer, oesophageal squamous cell carcinoma, renal cell carcinoma	EML
Addition of nivolumab for treatment of metastatic: gastric or gastro-oesophageal junction adenocarcinoma, oesophageal squamous cell carcinoma	EML
Addition of durvalumab for treatment of metastatic biliary tract cancer, endometrial cancer, hepatocellular carcinoma	EML
Addition of atezolizumab for treatment of metastatic hepatocellular carcinoma	EML
Addition of durvalumab and tremelimumab (as combination treatment) for treatment of metastatic hepatocellular carcinoma, non-small cell lung cancer.	EML
Addition of dostarlimab for treatment of metastatic endometrial cancer	EML
Addition of tislelizumab for treatment of metastatic non-small cell lung cancer, oesophageal squamous cell carcinoma	EML
Addition of sugemalimab for treatment of metastatic non-small cell lung cancer	EML
Addition of toripalimab for treatment of nasopharyngeal carcinoma, oesophageal squamous cell carcinoma	EML
Addition of glucagon-like peptide 1 (GLP-1) receptor agonists for the treatment of obesity	EML
Addition of amitriptyline for the new indication of migraine prophylaxis	EML
Addition of bisoprolol for the new indication of migraine prophylaxis as a therapeutic alternative to propranolol	EML

Table 4 *continued*

New medicines/indications	
Addition of fremanezumab for prophylaxis in high-frequency and chronic migraine	EML
Addition of risdiplam for treatment of spinal muscular atrophy	EML & EMLc
Addition of carbamazepine for the new indication of treatment of trigeminal neuralgia	EML
Addition of imipenem + cilastatin + relebactam for treatment of multidrug-resistant infections	EML
Addition of ciclopirox hydroxypropyl chitosan for treatment of onychomycosis	EML
Addition of hypochlorous acid for the new indications of antisepsis and wound management	EML & EMLc
Addition of panitumumab for the treatment of KRAS wild type metastatic colorectal cancer	EML

EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for Children.

Table 5
Changes to the AWaRe classification of antibiotics

Antibiotic	AWaRe classification
Azanidazole	Access
Amoxicillin + sulbactam	Access
Aztreonam + avibactam	Reserve
Benzathine phenoxymethylpenicillin	Access
Benzylpenicillin + procaine benzylpenicillin + benzathine-benzylpenicillin	Not recommended
Cefuroxime + metronidazole	Not recommended
Gepotidacin	Watch
Metronidazole + diloxanide	Not recommended
Metronidazole + furazolidone	Not recommended
Nalidixic acid (oral)	Watch
Nimorazole	Access
Norfloxacin + tinidazole	Not recommended
Ofloxacin + nitazoxanide	Not recommended
Ofloxacin + tinidazole	Not recommended
Paromomycin (oral)	Watch
Penicillins in combinations with other antibacterials	Not recommended
Pivampicillin + pivmecillinam	Not recommended
Propenidazole	Access
Satranidazole	Access
Sulfacarbamide + sulfadiazine + sulfadimidine	Not recommended
Sulfonamides in combinations with other antibacterials (excluding trimethoprim)	Not recommended
Tetracycline + chlortetracycline + demeclocycline	Not recommended
Tetracycline + nystatin	Not recommended
Ticarcillin + clavulanic acid	Watch
Tinidazole + diloxanide	Not recommended

List of participants

Expert Committee members

Loice Achieng Ombajo, Infectious disease specialist and senior lecturer, Department of Medicine and Co-director of the Center for Epidemiological Modelling and Analysis, University of Nairobi, Nairobi, Kenya.

Elie Akl, Professor of Medicine and Vice Provost for Research, American University of Beirut, Beirut, Lebanon.

Rita Banzi, Clinical pharmacologist, head of the Centre for Health Regulatory Policies, Mario Negri Institute, Milan, Italy.

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Elisabeth de Vries, Professor of Medical Oncology, University Medical Center Groningen, Groningen, Kingdom of the Netherlands.

Bishal Gyawali, Medical Oncologist and associate professor in medical oncology and public health sciences, Queen's University, Kingston, Canada.

Patrick Okwen, District medical officer and health economist; Team lead at Effective Basic Services Africa (eBASE), Bali, Cameroon.

Claudia Garcia Serpa Osorio de Castro, Pharmacist, Professor and Senior Researcher in Public Health, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.

Gabriela Prutsky Lopez, Assistant Professor of Pediatrics and pediatric hospitalist, Mayo Clinic, Mankato, United States of America; co-founder of Unidad de Conocimiento y Evidencia (CONEVID), Universidad Peruana Cayetano Heredia, Lima, Peru.

Andrew Roberts, Clinical Haematologist, Royal Melbourne Hospital and Peter MacCallum Cancer Centre; Professor and deputy director, the Walter & Eliza Hall Institute; Metcalf Chair of Leukaemia Research, University of Melbourne, Melbourne, Australia.

Zoubida Tazi Mezalek, Professor of Internal Medicine and Head of the Clinical Hematology Department, Faculty of Medicine and Pharmacy, Mohammed V University of Rabat, Rabat, Morocco.

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Nathália Alvarez, Intern, EML Secretariat, Department of Health Product Policy and Standards, Access to Medicines and Health Products.

External invited presenters during the Open Session

Michael Muenzberg, Chief Executive Officer, Targeted Solutions AG, Zug, Switzerland.

Declaration of interests

To be effective, the work of WHO and the contributions of its experts must be, and must be perceived to be, objective and independent. In this regard, to ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential or reasonably perceived conflict of interest related to the subject of the activity in which they will be involved. Declarations of interests and management of any disclosures is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). More information on WHO's policy on declarations of interest is available on the WHO website (*6*).

Before being invited to participate in the 25th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, all experts submitted written declarations of interest. In reviewing and assessing these declarations, the Secretariat of the WHO Essential Medicines List sought the advice of the Office of Compliance, Risk Management and Ethics.

The declaration of interest process resulted in the participation of the Expert Committee Members, Temporary Advisers, and invited external speakers during the Open Session, as reported in the list of participants.

Experts who declared having no conflicts of interest were Elie Akl, Rita Banzi, Francesco Ceppi, Patrick Okwen and Gabriela Prutsky-Lopez.

The following experts disclosed interests, which were assessed by the Secretariat for actual or potential conflicts and management strategies (if required).

Committee members

Loice Achieng Ombajo disclosed receiving honoraria from GSK to serve on a scientific advisory board for the Africa Open Lab research programme, supporting the selection of high-quality infectious diseases research proposals that have the potential to deliver significant health impact in Africa (interest ceased in 2024). She disclosed having received honoraria from Merck Sharp and Dohme for speaker engagements and conference travel on topics not related to medicines under evaluation at this meeting (interest ceased in 2024). The latter payment was below the threshold of significant financial interest. She disclosed funding to her institution (University of Nairobi) from ViiV Healthcare and Gilead Sciences for investigator-initiated clinical trials on medicines for HIV, for which she is the principal investigator. The three trials investigated switching between antiretroviral treatments (i.e. bictegravir, emtricitabine and tenofovir alafenamide to dolutegravir/lamivudine; ritonavir-boosted protease inhibitor regimen to dolutegravir; antiretroviral regimen to bictegravir, emtricitabine, and tenofovir alafenamide). These trials do not include antiretroviral treatments under evaluation at this meeting. Dr Achieng Ombajo is the clinical lead of a country grant programme to improve surveillance of *Candida auris* in Kenya (funded by the United States Centers for Disease Control and Prevention). She also disclosed funding to the university from the Gates Foundation for studying optimal management of dolutegravir failure and for epidemiological modelling and analysis. These disclosures were considered minor and did not require further management. Dr Achieng Ombajo currently serves as the Chair of the WHO Technical Advisory

Group on AWaRe (TAG-AWaRe) and was involved in the TAG-AWaRe's evaluation of antibiotic applications under consideration at the Expert Committee meeting. This position is unpaid. This disclosure was considered not to represent a conflict.

Elisabeth de Vries disclosed that she served as an expert in data safety monitoring committees for an ongoing trial investigating atezolizumab in adjuvant breast cancer sponsored by a non-profit research programme (National Surgical Adjuvant Breast and Colon Project) and for a completed trial investigating trastuzumab deruxtecan in advanced breast cancer sponsored by a for-profit company (Daiichi Sankyo). She also disclosed that she provided advice to Crescendo Biologics on improving the quality of the design and conduct of preclinical and phase I clinical studies exploring biological activity of bispecific molecules for the treatment of cancers. Sponsors provide funding to Dr de Vries' institution (University Medical Center Groningen) to cover her time commitment. She also disclosed that her institution is involved in early-phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution receives institutional funding from Amgen, Crescendo Biologics, Genentech, G1 Therapeutics, Regeneron, Roche, and Servier. In two cases, the studies involved using medicines under evaluation at this meeting (atezolizumab and cemiplimab). However, these studies as well as the others, assessed radioactive tracers used in imaging tests to monitor disease progression in patients with solid tumours, and did not involve assessment of medicines. Payment was made to the institution, and no personal salary support was received. These disclosures were considered to be unrelated, or not directly related, to the subject matter of the Expert Committee meeting and did not require further management. Regarding public statements and positions, Professor de Vries disclosed that she is a member of the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) working party and of the ESMO Cancer Medicines Working Group and was a member of the Response Evaluation Criteria in Solid Tumours (RECIST) Committee. These disclosures were considered not to represent a conflict of interests.

Claudia Garcia Serpa Osorio de Castro disclosed that she has received grant funding for consultancy work from Oswaldo Cruz Foundation Funding Agency to support a project on litigation for access to high-cost medicines sponsored by the Brazilian Ministry of Health, and research grant funding from the Brazilian National Council for Scientific and Technological Development. She also disclosed being a member of the Medicines Registration Technical Committee at the Brazilian Health Regulatory Agency, Anvisa, an unpaid position. These disclosures were considered not to represent a conflict and did not require further management.

Bishal Gyawali disclosed receiving consult fees from Vivio Health, a public benefit company, to provide patient-specific advice on treatment strategies. He declared having held stock options of OneCell Diagnostics (a liquid biopsy technology company, now divested). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Zoubida Tazi Mezalek disclosed receiving honoraria below the threshold for significant financial interest from pharmaceutical companies for participating in advisory boards on herpes zoster vaccine (GSK) and asciminib for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Novartis). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Andrew Roberts disclosed collaboration with BeiGene and research support to his institution from BeiGene for studies evaluating zanubrutinib, a medicine under evaluation at this meeting. These collaborations date back more than 4 years (i.e. 2014), the current limit to which the WHO's conflict of interest assessment extends. Nevertheless, this disclosure was assessed in detail. The first study (NCT02343120) is a phase I study in patients with relapsed/refractory B-cell malignancies, receiving dose-escalating zanubrutinib (*7*). The study primarily assessed safety, tolerability and pharmacokinetics/pharmacodynamics. A second study (NCT02343120) evaluated zanubrutinib in a phase I/II study in patients with Waldenström macroglobulinaemia (*8*). Subsequently, data from this trial were included in a safety analysis of zanubrutinib based on data from six pooled studies (*9*). The long-term monitoring phase of the study, to follow up surviving enrolled participants on the trial, will cease in 2025, as per standard practice in this type of study. Given the distant timing and the fact that the studies were phase I/II or focused on the safety and toxicity of zanubrutinib, and that none of the identified studies was used to support the request of the application received, this disclosure, made verbally at the start of the meeting, was considered minor and did not require further management.

Professor Roberts disclosed that he receives financial benefit from his employer, the Walter and Eliza Hall Institute (WEHI), in the form of a share of the income the Institute has received related to the drug venetoclax. Venetoclax was created during a partnership between WEHI and the pharmaceutical companies AbbVie and Genentech. AbbVie and Genentech are responsible for the commercial development of venetoclax. WEHI has no role in its clinical trial development, commercialization or marketing. WEHI has a commercialization policy that allows distribution of a small share of any royalties and commercial income to staff who have invented or made a major contribution to the product. The amounts received by individual staff are based on specific criteria related to their contributions and are not related to the outcome of clinical trials, nor to future drug sales. In 2017, WEHI entered a commercial agreement with CPPIB Credit Europe S.à r.l., a wholly owned subsidiary of the Canada Pension Plan Investment Board, trading future venetoclax royalties for a lump-sum payment. Professor Roberts disclosed that he was a major contributor to research that led to venetoclax, but is not a patent holder, and to early clinical trial discovery research. His contributions pre-date the 2017 commercial agreement with the Canadian pension fund. For his contribution, he has been awarded a small fraction of past commercial income to WEHI, which is diversified, independently managed and paid by his employer. Venetoclax was not under evaluation by the Expert Committee at this meeting, but it can be used as an alternative to or as a partner in combination with inhibitors of Bruton tyrosine kinase (e.g. ibrutinib, already included in the EML, and zanubrutinib, under evaluation during the meeting). Any interest or interests that could directly influence, or could appear to influence, his professional judgement in relation to the subject matter of the Expert Committee meeting were not identified.

Professor Roberts disclosed he is the chair of the Life Saving Drugs Program Expert Panel which advises the Australian Government on the appropriateness of public subsidy for medicines to treat patients with ultrarare conditions that are not considered cost-effective at the time of the evaluation. He also disclosed that in 2023 and 2024 he served on the Health Technology Assessment Review Reference Committee appointed by the Australian Government to provide

recommendations about the conduct of health technology assessment in Australia. Both positions are remunerated. These disclosures were considered not to represent a conflict and did not require further management.

Indah Widyahening disclosed that her institution received a research sponsorship from PT Sarihusada Generasi Mahardhika, a nutritional products company, for a study of growth tracker using artificial intelligence. This disclosure was considered minor and did not require further management.

Mei Zeng disclosed receiving research support for her research unit from Shanghai Roche Pharmaceuticals Ltd for a clinical trial of baloxavir marboxil in paediatric and adolescent patients with influenza. Her role in the study is lead principal investigator. This trial did not include medicines under evaluation at this meeting. This disclosure was considered minor and did not require further management.

Temporary advisers

Alfonso Iorio disclosed receiving research support for his institution, McMaster University, from F. Hoffmann-La Roche Ltd for an observational study on the long-term effectiveness and safety of emicizumab in people with haemophilia A based on the Canadian Hemophilia Bleeding Disorders Registry. Emicizumab is a medicine under evaluation at this meeting. This disclosure was considered minor. As a temporary adviser to WHO during the Expert Committee meeting, Professor Iorio participated in the discussion about medicines and blood products used in bleeding disorders but did not participate in the decision-making nor in formulating the recommendations on emicizumab.

Melissa Barber reported employment as a consultant for Medicines Sans Frontières. This disclosure was considered not to represent a conflict. As a temporary adviser to WHO during the Expert Committee meeting, Dr Barber participated in discussions about market analyses of medicines under evaluation but did not participate in the decision-making nor in formulating the recommendations.

Invited external speakers during the Open session

Michael Muenzberg declared having provided consultancies to advance affordable medicines, collaborating with regulators and suppliers from low- and middle-income countries. All consultancies were unpaid. He declared that in 2024 he funded a Switzerland-based platform to support global access efforts to medicines, with a primary interest in biosimilars.

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[1] All references in the report were last accessed on 25 June 2025.

1. Introduction

The meeting of the 25th WHO Expert Committee on the Selection and Use of Essential Medicines took place at WHO headquarters in Geneva, Switzerland, from 5 to 9 May 2025. The aim of the meeting was to review and update the 23rd WHO Model List of Essential Medicines (EML) and the 9th WHO Model List of Essential Medicines for Children (EMLc), the "Model Lists". The meeting agenda included 59 applications, including 31 proposals for the addition of new medicines or medicine classes, 10 proposals for new indications for currently listed medicines, three proposals for the addition of new formulations of currently listed medicines, one proposal for the removal of a currently listed medicine and 14 other applications relevant to the Model Lists and the WHO AWaRe classification of antibiotics.

The meeting was opened by Mr Deusdedit Mubangizi, Director, Health Products Policy and Standards Department, on behalf of WHO Director-General, Dr Tedros Adhanom Ghebreyesus. Mr Mubangizi welcomed Committee members and other meeting participants. He recognized that their participation underscored their belief in science-based policy and normative decision-making, as well as their commitment to multilateralism and solidarity.

In his opening remarks, Mr Mubangizi highlighted that the Expert Committee meeting comes at a time of profound uncertainty and shared concern for global public health. The recent indication by some Member States of their intent to withdraw from WHO and halt funding presents significant challenges. However, it also underscores the importance of solidarity, transparency and commitment to the collective mission of protecting and promoting health for all.

Mr Mubangizi shared some reflections on the role of the WHO EML in supporting global access to medicines. The first was on the temporal positioning of the EML in relation to the life cycle of medicines, from when a medicine first comes to market and is used in clinical practice, to when it may be superseded by newer, more effective and safer medicines. Before 2000, WHO, with the support of this Committee, reviewed and recommended medicines for the EML that had been on the market and well established in clinical practice for several years. These recommendations primarily concerned generic medicines, which were often already widely available when EML listing was recommended. Since 2000, there has been a shift. EML listings moved towards the earlier part of the life cycle of medicines, initially only for medicines against infectious diseases such as human immunodeficiency virus. Subsequently, this shift has also extended to medicines in other disease areas. At the same time, the life cycle of medicines has become more complex, encompassing entire pharmaceutical classes in which several generations of medicines follow one another. At this meeting, the generational perspective involving the same pharmacological class is seen in

several applications. For leukaemia, there is the request to include zanubrutinib, a second-generation Bruton tyrosine kinase inhibitor, following the listing in 2021 of first-generation ibrutinib; for diabetes, there is a request to include more insulin analogues to complement human insulin; for cancers, there are requests to include immune checkpoint inhibitors encompassing first-, second- and third-generation medicines. The Expert Committee is charged with the task of making evidence-based recommendations to WHO, while also considering key public health issues. Finding the right balance between the evidence, public health relevance, feasibility, innovation, and sustainable and affordable access will be a challenge.

The second reflection concerned diseases for which the EML currently offers no treatment options. Mr Mubangizi reinforced the importance of timely decisions of the Expert Committee to recommend, or not, first-in-class therapies. For example, the Expert Committee's decision to recommend listing some medicines for multiple sclerosis in 2023 made it possible to provide patients with earlier access to these life-changing therapies and responded to significant unmet medical needs. Following this decision, rituximab is now reimbursed for multiple sclerosis in Thailand and Zambia. Mr Mubangizi highlighted that in this update, there are three diseases for which the EML currently has no medicines: two are rare diseases (cystic fibrosis and spinal muscular atrophy) and the other is obesity, which affects hundreds of millions of people. It will be another challenge to find and balance solutions across such different conditions.

Mr Mubangizi's final reflection showcased the role of the EML in catalysing other actions to improve access, and gave the example of the change from inexpensive antimalaria treatment with chloroquine to much more expensive artemisinin-based combination therapy. The inclusion of artemisinin-based treatments on the EML signalled the public health importance these therapies, particularly in the face of increasing resistance to chloroquine. Thereafter, artemisinin-based therapies were incorporated into malaria treatment guidelines, and within 3 years, the cost of these therapies had more than halved.

Mr Mubangizi concluded his remarks by thanking Committee members for their time and commitment in supporting WHO with its continuing work on selection and use of essential medicines and wishing them a fruitful and successful meeting. He acknowledged that it would take time to implement the recommendations that come out of the meeting, as EML listing is only one step on the path to access. He affirmed that WHO is ready to take that step and to work across the Organization and with its partners on the other steps to achieve our shared goal of health for all.

2. Open session

The open session of the meeting was held in person and virtually and was chaired by Deus Mubangizi, Director, Department of Health Product Policy and Standards on behalf of the Director-General. It was attended by a variety of interested parties including representatives of WHO Member States, nongovernmental organizations, academia and civil society.

Updates from the WHO Secretariat were presented by: Lorenzo Moja, Essential Medicines Team Lead a.i.; Ana Aceves Capri, Essential Diagnostics List Secretariat; Martina Penazzato, Global Accelerator for Pediatric Formulations (GAP-f) Secretariat; and Roberta Ortiz, Global Initiative for Childhood Cancer.

Chairs of the EML Cancer Medicines Expert Group (Elisabeth de Vries) and the WHO Technical Advisory Group on AWaRe (Loice Achieng Ombajo) presented updates on the work undertaken by these groups since the previous Expert Committee meeting.

Three speakers were invited to give presentations on topics of relevance to the current and ongoing work of WHO on essential medicines: Kalipso Chalkidou, Director of the WHO Department of Health Financing and Economics, presented on medicines markets in low- and middle-income countries and considerations from health financing and economics perspectives. Rebekah Thomas, Technical Officer in the WHO Quality, Norms and Standards Department, presented on the evolution of WHO guideline development methods. Michael Muenzberg, Chief Executive Officer of Targeted Solutions presented on the role of biosimilars in advancing EML recommendations and transforming access.

Stakeholder statements were delivered by the following participants.

- Angela Nwokoh, Albinism Association of Nigeria
- George Pentheroudakis, European Society for Medical Oncology
- Fernando Pascuql Martinez, Global Antibiotic Research and Development Partnership
- Nupur Lalvani, Indian Diabetes Organizations
- John Coughlan, International Cerebral Palsy Society
- Sergio Cavalheiro Filho, International Federation of Pharmaceutical Manufacturers and Associations
- Esin Kandemir, International Society of Oncology Pharmacy Practitioners
- Thiru Balasubramanian, Knowledge Ecology International
- Candice Sehoma, Médecins Sans Frontières
- Giulia Segafredo, Medicines Patent Pool
- Joanna Laurson-Doube, Non-communicable Diseases Alliance

- Chiu-Hui (Mary) Wang, Rare Diseases International
- Gayle Pledger and Ajsela Kushova, Right to Breath Campaign, Vertex Save Us, Just Treatment
- Chris Toavs, T1 International
- Clara Maliwa, Dar es Salaam, United Republic of Tanzania
- Muluka-Anne Miti-Drummond, UN Independent Expert on the Enjoyment of Human Rights by Persons with Albinism
- Shalini Jayasekar Zurn, Union for International Cancer Control
- Radoslaw Kaczmarek and Clive Smith, World Federation of Hemophilia

Copies of all presentations and statements are available on the WHO website (*1*).

3. General items

Age-appropriateness of formulations of essential medicines for children

In consideration of the review of the age-appropriateness of formulations of medicines on the EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the report prepared by the Secretariat. Corresponding changes to the EML were made for consistency, as appropriate. All changes are reported in Tables 1, 2 and 3 of the Executive summary. The Committee also endorsed the proposals made in the review for consideration by the Global Accelerator for Paediatric Formulations (GAP-f) network where gaps in the availability of age-appropriate formulations of essential medicines for children were identified.

Revision of AWaRe definitions, and classification/reclassification of antibiotics

The Expert Committee considered the applications proposing:

- a revision of the current Access, Watch and Reserve (AWaRe) definitions for AWaRe classification and criteria for inclusion of AWaRe antibiotics on the Model Lists;
- classification of antibiotics not currently included in the WHO AWaRe classification database; and
- reclassification of cefoperazone + sulbactam from "not recommended" to the AWaRe Watch group.

The Committee acknowledged the growing importance and adoption of AWaRe as a global tool for antibiotic stewardship, surveillance and policy development, and its strong relationship with the WHO Model Lists of Essential Medicines.

The Committee noted that the definitions of AWaRe groups were developed between 2017 and 2019, reflecting the evaluation of antibiotics that were recommended for inclusion in the Model Lists. The Committee accepted that the current definition of Reserve antibiotics – intended for use as last resort options in life-threatening infections due to multidrug-resistant bacteria – should adapt to the needs of changing public health policies and priorities. The Committee considered that there were several aspects of the current definition that could evolve, expand or be modified. These include expanding guidance on

the level of evidence required to demonstrate so-called proven activity against WHO priority pathogens, clarifying whether the relationship between the Reserve definition and the WHO Bacterial Priority Pathogens List is binding, and developing standardized definitions for multidrug resistance. The Committee also recognized the limited clinical evidence available to guide empiric use of Reserve antibiotics, particularly in low-resource settings. The Committee determined that there was also a need to consider additional dimensions in the selection of Reserve antibiotics for the Model Lists, including innovation criteria, access challenges and the role of real-world evidence.

The Committee noted a growing debate about how the definition of Reserve antibiotics should evolve. The Committee also noted the comments of the WHO Technical Advisory Group on AWaRe (TAG-AWaRe) calling call for a comprehensive reassessment of all AWaRe categories, with the establishment of clear criteria for AWaRe classification groups. This reassessment should consider dimensions such as efficacy, safety, impact on the emergence and spread of resistance, and impact on the microbiome. It should also link to other WHO products, including (but not limited to) the Bacterial Priority Pathogens Lists, the Medically Important Antimicrobial List, and the report of antibacterial agents in clinical and preclinical development.

Considering the complexity of the challenges posed in refining definitions for all AWaRe categories, the Expert Committee requested the WHO Secretariat to coordinate a structured, inclusive review process, involving broad stakeholder consultation and a review of available evidence, with the aim of strengthening the AWaRe framework as a cornerstone of global antimicrobial stewardship and access policy. The recommendations of this review should be submitted for consideration by the 2027 Expert Committee. Therefore, the Committee did not recommend any changes to the current AWaRe definitions.

Consequently, until such time as the definitions of AWaRe categories are revised, the Committee did not recommend any change to the current classification of cefoperazone + sulbactam. The Committee also noted that numerous other beta-lactam + beta-lactamase inhibitor combinations are also currently classified as "not recommended" and considered that reclassifying only one such combination at this time would introduce inconsistency.

In consideration of the request to classify antibiotics not currently included in the AWaRe classification, the Expert Committee accepted the rationale presented in the application and recommended that the antibiotics it identified be classified as Access, Watch, Reserve, not recommended, or remain unclassified, as proposed (Table 5 of the Executive summary).

Commemoration of the 50th anniversary of the WHO Model List of Essential Medicines in 2027

The Expert Committee noted the report of the meeting on revising the procedures for updating the Model Lists of Essential Medicines, convened by WHO in Geneva in November 2023 (*2*). The Committee welcomed and endorsed all key messages that emerged during the meeting.

- The importance of strengthening alignment and integration of the EML with related WHO guidelines and products to reduce redundant efforts, mitigate contradicting messages and facilitate coordinated evidence-based policy-making. To achieve this goal requires harmonizing procedures, identifying situations of potential discordance and addressing incidents of disharmony.
- The importance of improving dissemination strategies related to the selection of medicines, including publishing information not only about medicines that are listed but also those that have not been recommended for listing. Rejections can be informative, as medicines rejected for addition to the EML might have problems of efficacy and safety, equity, feasibility, cost–effectiveness or access, with implications for national EMLs.
- The value of developing a structured process for prioritizing disease areas and medicines for EML applications to ensure an orderly, proactive approach, particularly for overlooked disease areas. Coordinated applications could be developed by utilizing partnerships with professional societies.
- The need to improve the extent and quality of information on price, cost and cost–effectiveness considered in EML selection. Among other strategies this involves incorporating data on pricing of medicines (including generics and biosimilars and their availability) and understanding the financial impact on patients (i.e. out-of-pocket expenditure).
- Modernizing and investigating resources that can help the selection process. Electronic support systems such as digital submission form, artificial intelligence to increase efficiency and precision in administrative processes, and more human resources to enable the Secretariat to improve quality of the selection process were proposed.
- The need to ensure sustained progress on improving access requires tackling systemic barriers beyond medicine selection. It is crucial to study the accessibility of certain medicines once they have been listed on the EML or EMLc to see if being on the list has

contributed to improved access. It is also important to understand the role of pricing opacity, production barriers that limit availability of generics, inconsistent supply and delivery, and inappropriate marketing influences.

The Committee considered that many of these recommendations relate directly to activities that address WHO's mandate to assist Member States by advising on the selection and procurement of essential medicines that offer the best value health outcomes.

The Committee highlighted that the 50th anniversary of the EML provides a valuable opportunity for Member States to actively participate in commemorating the WHO EML and recognizing its impact on national policies and essential medicines lists. The Committee considered that updates of national lists in 2027 should be a central activity of the commemorations. These updates should not be aimed solely at adding new medicines to national lists but should also aim to achieve greater alignment between national EMLs and national reimbursement lists, with transparent reporting of what is made available as part of universal health coverage policies. Consideration should be given to strengthening national EMLs by developing lists that specify the indications for which medicines are considered essential.

Other important elements of the updates to national EMLs for the commemoration include:

- transparent inclusion of medicines and age-appropriate formulations for children. disappointingly; less than 15% of countries prioritize medicines and formulations for children in their national lists (3);
- clear reporting of priority formulations to guide supply and procurement, and limit fragmentation;
- optimizing interpretation and implementation of therapeutic alternative guidance (square box listings) in the WHO EML.

The 50th anniversary of the EML is an opportunity for Member States to reaffirm the fundamental right to access essential medicines. By participating in the celebration, updating national tools, promoting public engagement and strengthening policies, countries can help ensure that essential medicines remain a living, evolving and effective instrument for health equity.

Improving the quality of EML applications

The Expert Committee noted a general improvement in the quality of applications under evaluation at the current meeting, although considerable variability remained between applications.

The Committee expressed appreciation for the open and participatory nature of the application process, where applications may be submitted by individuals, institutions, public and private sector organizations and other stakeholders. However, in many cases, applications are developed on an ad hoc and voluntary basis and sometimes lack sufficient scientific rigour (e.g. management of inherent biases), fail to present benefits across different patient subgroups, and often lack comprehensive analyses of feasibility, cost–effectiveness and budget impact in different settings. The Committee considered that applications for the EML would benefit from following a process similar to that of WHO's guideline development processes, which should also facilitate alignment of the recommendations in these two WHO tools, and orient selection and appropriate use of medicines recommended by WHO.

The Committee commended two applications as exemplifying a high standard of scrutiny and comprehensive evaluation of multiple therapeutic options within specific disease areas: the 2023 application proposing essential medicines for the treatment of multiple sclerosis (*4*) and the 2025 application proposing PD-1/PD-L1 immune checkpoint inhibitors for various cancers (*5*). These applications were the result of a coordinated effort by various entities, including academic groups, scientific societies, methodology support teams, and close collaboration with the EML Secretariat. Notable strengths were the use of a comprehensive, disease-focused strategy with clear prioritization criteria, rather than a narrower focus on individual medicines, and the systematic use of GRADE Evidence to Decision (EtD) tables to summarize the findings.

The Committee highlighted that the adoption of guiding decision-making frameworks to suit EML requirements, particularly the capacity of these frameworks to clarify how the magnitude of benefits varied across different therapeutic options and patient subgroups, greatly facilitated the Committee's decision-making. The Committee appreciated the efforts of the WHO Secretariat to better align the EML selection process with established guideline development tools, such as the GRADE EtD framework, to enhance transparency and assessment of the quality of evidence.

The Committee recommended the incorporation of EtD tables in EML applications going forward. However, the Committee recognized that it would take time for a methodological and reporting approach to become an integral part of the application process. Additionally, such requirement may exclude or discourage applicants without the necessary expertise or capacity to develop EtD tables from participating in the EML process, an outcome that should be avoided. The Committee considered that a possible way to reduce this risk would be to develop a structured process for setting priorities for EML applications where applicant participation can be encouraged and supported by public health partners.

Finally, the Committee observed that the number of applications for newer, patented, highly priced medicines has grown considerably over time. The Committee considered that the voluntary nature of the current application process has the potential to create gaps in selection and coverage for other older (but no less important) medicines for which there may be less commercial interest. The Committee recommended WHO develop a strategy guided by priority needs to complement the existing application process to ensure applications for essential medicine candidates are submitted, regardless of their stage in the medicine life cycle.

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4. Summary of recommendations

Changes to sections of the Model Lists

Refer to Table 3 of the Executive summary for details of changes to sections and subsections of the Model Lists.

Additions to the Model Lists

Section 5.1.4: Baclofen is added to the complementary list of the EML and EMLc for the treatment of spasticity in cerebral palsy.

Section 6.4.2.5: Abacavir + dolutegravir + lamivudine is added to the core list of the EMLc for the treatment of HIV infection.

Section 7: Elexacaftor + tezacaftor + ivacaftor and ivacaftor are added to the core list of the EML and EMLc for the treatment of cystic fibrosis.

Section 8.2.3: Blinatumomab is added to the complementary list of the EML and EMLc for the treatment of B lineage acute lymphoblastic leukaemia. Pembrolizumab (with atezolizumab and cemiplimab as therapeutic alternatives) is added to the complementary list of the EML for the treatment of metastatic cervical cancer, metastatic colorectal cancer and metastatic non-small cell lung cancer.

Section 10.2: Emicizumab is added to the core list of the EML and EMLc for the treatment of haemophilia A with and without factor VIII inhibitors.

Section 11.3: Recombinant coagulation factors VIII and IX are added to the core list of the EML and EMLc for the treatment of haemophilia A and B, respectively.

Section 12.3: Amlodipine + perindopril + indapamide, and amlodipine + valsartan + hydrochlorothiazide (with within-class medicines as therapeutic alternatives) are added to the core list of the EML for the treatment of hypertension.

Section 13.4: Ustekinumab is added to the complementary list of the EML and EMLc for the treatment of moderate-to-severe psoriasis.

Section 13.6: Glycerol- and urea-based topical moisturizing creams are added to the core list of the EML and EMLc for treatment of atopic dermatitis.

Section 13.7: Broad-spectrum sunscreen is added to the core list of the EML and EMLc for the prevention of skin cancer in people with albinism.

Section 18.5.1: Rapid-acting insulin analogues (insulin aspart, insulin glulisine and insulin lispro) are added to the core list of the EML and EMLc for treatment of type 1 and type 2 diabetes.

Section 18.5.2: Semaglutide (with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives) is added to the core list of the EML for the treatment of type 2 diabetes in people with established cardiovascular or chronic kidney disease and with obesity.

Section 19.3: Ebola, hepatitis E, mpox and respiratory syncytial virus vaccines are added to the core list of the EML; Ebola, malaria and mpox vaccines are added to the core list of the EMLc.

Section 24.5.2: Cytisine is added to the core list of the EML for use in tobacco cessation.

Deletions from the Model Lists

The following medicines were deleted from the EML and EMLc:

- amodiaquine (single agent) for treatment of malaria
- coagulation factor IX complex as a therapeutic alternative to plasma-derived coagulation factor IX
- halothane as an inhalational anaesthetic
- proguanil for chemoprevention of malaria.

Refer to Tables 1 and 2 of the Executive summary for details of the deletion of specific formulations and/or strengths of listed medicines from the EML and EMLc, respectively.

New indications

Section 5.1.1: New indication of infantile spasm for prednisolone on the EMLc.

Section 5.1.5.1: New indication of acute migraine for ibuprofen on the EML. New indication of cluster headache for prednisolone, sumatriptan and verapamil on the EML.

Section 6.5.5.1: New indication of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* infection for fexinidazole on the EML and EMLc.

Section 13.4: New indication of moderate-to-severe psoriasis for adalimumab on the EML and EMLc.

Section 18.1: New indication of adrenal insufficiency for prednisolone on the EML and EMLc.

New formulations/strengths

Section 6.2.5: Inclusion of rifapentine 150 mg dispersible, scored tablets on the EMLc.

Section 10.2: Inclusion of phytomenadione injection mixed micelle solution 2 mg/0.2 mL and 10 mg/mL on the EML and EMLc.

Section 18.5.1: Inclusion of long-acting insulin analogues injection 100 IU/mL in 10 mL vials on the EML and EMLc.

Refer also to Tables 1 and 2 of the Executive summary for details of the addition of other new formulations/strengths of listed medicines on the EML and EMLc, respectively.

Other changes to listings

Refer to Table 3 of the Executive summary for details of other changes to the listings of medicines on the Model Lists.

Applications not recommended

Refer to Table 4 of the Executive summary for details of applications that were not recommended.

5. Applications for the 24th Model List of Essential Medicines and the 10th Model List of Essential Medicines for Children

Section 1: Anaesthetics, preoperative medicines and oxygen

1.1 General anaesthetics and oxygen

1.1.1 Inhalational medicines c

Halothane – deletion/retention – EML and EMLc

Halothane	ATC code: N01AB01

Proposal

Delay the recommended removal of halothane from the EML and EMLc until 2027.

While strongly advocating for phasing out of halothane in clinical practice, the applicants highlighted that halothane is no longer available in upper middle- and high-income countries. However, halothane continues to be used in low-resource settings due to its relatively lower cost and familiarity of anaesthesia providers with the medicine in such settings. The applicants argued that transitioning to new anaesthetic agents will require initiatives targeted to anaesthesia providers in low-resource setting, and sufficient time for ministries of health and finance to make appropriate budgetary allocations and purchase and implement operational aspects of supplying alternatives.

Applicant

World Federation of Societies of Anaesthesiologists

EML/EMLc

EML and EMLc

Section

1.1.1 Inhalational medicines

Dose form(s) & strengths(s)

Inhalation

Core/complementary

Core

Individual/square box listing

Individual

Background

In 2023, the Expert Committee considered an application from Abbvie Biopharmaceuticals GmbH for the addition of sevoflurane to the EML and EMLc as an inhalational gas for general anaesthesia. The Committee recommended the inclusion of sevoflurane on the core list of the EML and EMLc as an inhalational anaesthetic based on evidence of similar efficacy and safety to isoflurane, and a lower global warming potential than the currently listed alternatives.

In consideration of the volatile anaesthetics included on the Model Lists, the Committee noted that halothane is no longer used in many countries because of its harm profile. The Committee also noted that the price difference between halothane, isoflurane and sevoflurane has decreased since sevoflurane was previously considered for inclusion in the Model Lists in 2011. The Committee considered that more efficient use of sevoflurane in preference to halothane and isoflurane can contribute to reducing greenhouse gas emissions. In addition, given the limited role of halothane among anaesthetic gases, the Committee recommended that halothane be flagged for deletion from the Model Lists in 2025 without further discussion, unless an application was received in support of its retention.

Committee recommendations

The Expert Committee recalled the recommendation of the 2023 Expert Committee to remove halothane from the Model Lists in 2025 unless an application was received in support of its retention. This recommendation was based on halothane's limited role among anaesthetic gases and the availability and listing of safer alternatives on the EML and EMLc, which are associated with lower greenhouse gas emissions (e.g. sevoflurane).

The Committee considered the application from the World Federation of Societies of Anaesthesiologists to maintain listing of halothane until 2027 to allow more time for Member States in which halothane is still used to implement the change at the clinical, operational and budgetary levels. The application highlighted that halothane is still used in resource-constrained settings because of its relatively lower cost and because anaesthesia providers in such settings are familiar with its use.

The Committee acknowledged that in those settings where halothane is still used, phasing out and transitioning to the use of alternative anaesthetic agents is a stepwise and multifactorial process which may be lengthy. The Committee noted and welcomed the actions described in the application to support the phasing out of halothane and encouraged their timely implementation.

However, the Committee considered that it was appropriate to uphold the 2023 Committee's recommendation to remove halothane from the Model

Lists in 2025 to reinforce the importance of prioritizing alternative inhalational anaesthetic agents with a lower propensity for environmental impact and encourage necessary actions to achieve this change. The Committee acknowledged and accepted that some countries might continue to include halothane in their national essential medicines lists and that local circumstances may necessitate and justify its ongoing inclusion in these lists and use in clinical practice during a necessary transition period.

Therefore, the Expert Committee recommended the removal of halothane from the EML and EMLc to support efforts to reduce the impact of essential anaesthetic gases on climate change.

Nitrous oxide – change to listing – EML and EMLc

Nitrous oxide **ATC code: N01AX13**

Proposal

Addition of a qualifying statement to the listing of nitrous oxide on the EML and EMLc recommending use of point-of-care cylinder delivery systems of nitrous oxide over centrally supplied piped delivery systems to reduce atmospheric pollution and environmental impact.

The applicants highlight that nitrous oxide is a potent greenhouse gas and depletes ozone, with significant environmental impact. In most large health-care facilities, it is delivered from centrally located bulk storage tanks through pressure-regulated piping. However, reports suggest that a large proportion of nitrous oxide is lost through leaks in central piped systems, meaning only a small proportion is used clinically. This contributes to substantial waste that increases costs for health care systems, reduces supply chain resilience, increases occupational exposure risk, and damages the environment and human health. The use of small, portable nitrous oxide cylinders attached to individual anaesthesia machines at the point of care eliminates a significant amount of the nitrous oxide loss that occurs from central piped systems. The application argued that decommissioning/avoiding installation of bulk nitrous oxide piped systems and transitioning to a patient-level source for nitrous oxide delivery would substantially improve supply system efficiency and decrease costs and total health-care emissions, without eliminating or restricting the clinical use of nitrous oxide.

Applicant

World Federation of Societies of Anaesthesiologists

EML/EMLc

EML and EMLc

Section

1.1.1 Inhalational medicines

Dose form(s) & strengths(s)

Inhalation

Core/complementary

Core

Individual/square box listing

Individual

Background

Nitrous oxide has been included on the EML and EMLc since the first lists were published in 1977 and 2007, respectively.

Committee recommendations

The Expert Committee acknowledged that leakage of nitrous oxide from centrally supplied piped systems is responsible for substantial wastage for health-care facilities, atmospheric pollution and greenhouse gas emissions.

The Committee considered that minimizing system waste and adopting a nitrous oxide waste reduction strategy by transitioning to point-of-care cylinders and away from centrally piped infrastructure should be encouraged in national healthcare systems.

The Committee therefore recommended the inclusion of a note with the listing of nitrous oxide on the EML and EMLc indicating the preferred supply of nitrous oxide via point-of-care cylinders instead of centrally supplied (piped) delivery systems to support efforts to reduce the impact of essential anaesthetic gases on climate change.

Section 5: Medicines for neurological disorders

Changes to Section 5

The Expert Committee endorsed changes to Section 5 of the Model Lists, incorporating the suggestions made by Médecins Sans Frontières in the contribution received during the public consultation period. Additional changes to this section as a result of other recommendations made during the meeting are also endorsed. The changes are summarized in Table 3 of the Executive summary.

5.1 Medicines for central nervous system disorders

Risdiplam – addition – EML and EMLc

Risdiplam **ATC code: M09AX10**

Proposal

Addition of risdiplam to the core list of the EML and EMLc for the treatment of spinal muscular atrophy (SMA) in paediatric and adult patients.

Applicant

Knowledge Ecology International

WHO technical department

The Department of Mental Health, Brain Health and Substance Use reviewed and provided comments on the application. It highlighted that the feasibility of implementation and use of risdiplam in low-resource settings remains a challenge in that genetically confirmed SMA requires capacity and resources to diagnose and treat. These include specialist health-care workers, laboratories with diagnostic capabilities and health-care systems with strong supportive services. However, oral administration of risdiplam is especially suited for resource-constrained settings and given its potential to slow, halt or, in many cases, reverse disease progression, caregiver burden is likely to decrease with administration of this medication.

The WHO Department Maternal, Newborn, Child and Adolescent Health and Ageing supported the inclusion of risdiplam on the EMLc, highlighting that it is the only orally administered disease-modifying therapy currently available for SMA, and it may be the best choice in low- and middle-income countries.

EML/EMLc

EML and EMLc

Section

5 Medicines for neurological disorders

Dose form(s) & strengths(s)

Powder for oral solution: 0.75 mg/mL

Tablet (dispersible): 5 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

There are currently no treatments for SMA included on the EML and EMLc. Risdiplam was previously considered for inclusion on the EML and EMLc for the treatment SMA in paediatric and adult patients in 2023 (*1*).

The 2023 Expert Committee acknowledged that SMA was associated with considerable morbidity and mortality in affected children and adults. While it has a relatively low incidence in the general population, disease clusters are possible, particularly in families with increased prevalence of consanguinity. The Committee reaffirmed that the low incidence of a disease is not a factor on its own that precludes the inclusion of medicines on the Model Lists, and highlighted that essential medicines for rare diseases had been included since the first Model List was published in 1977 (e.g. blood coagulation factors for haemophilia and antirabies hyperimmune serum (later equine rabies immunoglobulin)).

The Committee noted the current availability of three treatments for SMA: one small molecule (risdiplam); one antisense oligonucleotide (nusinersen); and one gene therapy (onasemnogene abeparvovec). These treatments share some characteristics: they are associated with potentially important clinical benefits which appear to be greatest with the early introduction of treatment in presymptomatic infants who carry the survival motor neuron 1 gene (*SMN1*) gene mutation responsible for SMA, and in symptomatic patients with recent onset of symptoms; and they all have a high price. Between risdiplam and nusinersen, the Committee noted the greater feasibility of risdiplam over nusinersen. Nusinersen requires administration by intrathecal injection every 4 months which must be done in hospital by trained health professionals, while risdiplam is administered orally. Nusinersen also has adverse effects such as headache, vomiting, back pain and risk of infections.

The Committee noted that the body of evidence for efficacy and safety of risdiplam in SMA was still limited, with only a small number of patients

exposed to long-term treatment. The Committee noted that most patients had a disease duration of at least 3 months when they were enrolled in the clinical trials. About 50% of children treated with risdiplam showed improvement in motor function (e.g. sitting without support for ≥ 5 seconds) at 24 months, and more children achieved motor milestones with prolonged treatment. While risdiplam is likely associated with longer survival without the requirement for permanent mechanical ventilation, based on the available data, no participants could stand or walk alone when risdiplam had been given after disease onset. The Committee noted that based on the available evidence in patients with symptomatic disease, improvements in motor function were observed in younger children (< 5 years) but that these improvements became increasingly less noticeable in older children, adolescents and adults. Treatment-related adverse effects were generally mild. Overall, the Committee considered that the magnitude and long-term duration of benefits and potential harms of risdiplam were still uncertain.

The Committee noted that newborn screening for SMA had been introduced into routine screening panels in some high-income countries in recent years. However, the effectiveness of such screening programmes in identifying potential patients in a presymptomatic stage of the disease had not yet been assessed. The Committee also noted the preliminary results of ongoing clinical trials of risdiplam in presymptomatic infants up to 6 weeks of age. As risdiplam is likely to be associated with larger benefits when treatment is started before symptom onset, the Committee considered that it would be important to study its long-term effectiveness in those settings where routine newborn screening programmes for SMA are implemented.

The Committee advised that data on SMA screening programmes and use of risdiplam in presymptomatic infants should be reviewed as they become available, as well as the outcomes of longer-term clinical trials for risdiplam in older, less severely affected, symptomatic patients.

The Committee noted the current high price of risdiplam and that reimbursement decisions in some high-income countries have been made subject to managed entry arrangements or price reduction, and that generic versions of risdiplam were not currently available. The Committee noted that a request made by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam had not been granted by the patent holder. Nevertheless, the Committee considered that risdiplam could be flagged to the Medicines Patent Pool as a potential candidate for negotiating public health-oriented licences to facilitate affordable access in low- and middle-income countries.

Based on these considerations, the 2023 Expert Committee did not recommend listing risdiplam.

Public health relevance

SMA is an autosomal recessive genetic disease characterized by the degeneration of lower motor neurons in the spinal cord. It is caused by deletion or mutation of the *SMN1* gene, which codes for the survival motor neuron protein, a protein critical for motor neuron survival. Symptoms include skeletal muscle atrophy, progressive generalized weakness and respiratory failure, potentially leading to early death (2, 3).

The disease has been divided into five types, based on age at symptom onset and maximum motor function achieved in untreated patients (4). Type 0 is a rare and severe type of SMA with symptoms beginning before birth. At birth, the infant presents with severe weakness and difficulty in breathing and feeding. Type 1 is the most common form of the disease and symptom onset is before 6 months of age, with children presenting with severe muscle weakness and trouble breathing and swallowing. Type 2 is noticed between 6 and 18 months of age and children with this type can usually sit without support but are unable to stand or walk without help. Type 3 shows symptoms after 18 months of age and children normally can walk independently but have difficulty doing so, and they may have trouble running, rising from a chair or climbing stairs. Type 4 develops after 18 years of age and symptoms include mild to moderate leg muscle weakness (5).

The incidence of SMA has been estimated at around 1 in 10 000 live births, with a prevalence of about 1–2 per 100 000 people. Since SMA is a rare condition, studies of its prevalence and incidence are challenging, and the numbers vary across populations (6).

SMA is the most common monogenic cause of death among infants (3). For SMA type 1, in the absence of treatment, the mortality rate is greater than 90% by 2 years of age (4). Due to decreasing physical abilities, motor functions and potential death caused by the disease, patients and families often experience a substantial psychological and emotional burden (7).

Apart from risdiplam, two other medicines are available for the treatment of SMA: nusinersen and onasemnogene abeparvovec. Nusinersen is an antisense oligonucleotide administered via intrathecal injection, which requires a hospital setting. It is not suitable for patients with spinal deformities, scoliosis or previous scoliosis surgery, which are common in patients with the disease. Onasemnogene abeparvovec is a gene therapy administered through a one-time intravenous infusion, also requiring a hospital setting. In contrast, risdiplam is an oral medicine that can be administered at home and does not require hospitalization. SMA patients have at least one copy of the survival motor neuron 2 gene (*SMN2*), which produces an unstable form of survival motor neuron protein. Both risdiplam and nusinersen target this gene, while onasemnogene abeparvovec acts on gene *SMN1*. All three medicines are considered to have a high cost (8). None of these therapies is a cure for SMA.

Summary of evidence: benefits

Risdiplam has been evaluated in three clinical trials: RAINBOWFISH, FIREFISH and SUNFISH.

RAINBOWFISH is a pharmaceutical-company-funded, open-label, single-arm, multicentre clinical study of the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in presymptomatic infants aged from birth to 6 weeks who have been genetically diagnosed with SMA with 2, 3 or ≥ 4 copies of *SMN2*. A total of 26 participants were enrolled in the intention-to-treat population, aged between 16 and 41 days. Median age at first dose was 25 days. Eligibility criteria included the absence of the need for invasive ventilation, tracheostomy or awake non-invasive ventilation, and absence of concomitant or previous administration of other medicines targeting *SMN2* or gene therapy. The primary efficacy endpoint was the proportion of the primary efficacy population (infants with 2 *SMN2* copies and compound muscle action potential amplitudes ≥ 1.5 mV at baseline, $n = 5$) able to sit without support for ≥ 5 seconds at 12 months. Secondary endpoints (all participants) included: percentage of participants who develop clinically manifested SMA; time to permanent ventilation and/or death; percentage of participants who are alive without permanent ventilation; percentage of participants who achieve motor milestones; motor function measures; growth measures; nutritional status; and additional clinical parameters. Updated results since the data presented in the previous application have been reported in conference proceedings after 12 and 24 months of treatment.

Two-year data from RAINBOWFISH were presented at the World Muscle Society Annual Congress in October 2024 (*9*). A total of 23 infants completed 24 months of treatment. At 24 months, all infants with 2 *SMN2* copies ($n = 5$) could sit without support, 3/5 (60%) could stand alone and 3/5 (60%) were able to walk independently. Among infants with 3 *SMN2* copies ($n = 13$), 12/13 (92%) could sit without support for ≥ 30 seconds, and all could stand alone and walk independently. Among infants with ≥ 4 *SMN2* copies ($n = 5$), 4/5 (80%) could sit without support for ≥ 30 seconds and all could stand alone and walk independently. Most infants with 3 or ≥ 4 *SMN2* copies were able to achieve age-appropriate motor milestones within windows of achievement established by the WHO Multicentre Growth Reference Study Group (*10*). Clinically manifested SMA was reported in 6/26 (23%) infants, all of whom had 2 *SMN2* copies. All infants who completed 24 months of treatment were able to speak and maintained swallowing and feeding abilities. None required permanent ventilation. After 24 months of treatment, cognitive skills typical of normal child development were reported.

FIREFISH was a company-sponsored, open-label, multicentre study to investigate safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics

of risdiplam in infants with symptomatic type 1 SMA and age between 1 and 7 months. The study was divided in two parts, an exploratory dose-finding part (part 1) and a confirmatory part (part 2) to investigate the treatment with the dose selected in the first part.

In FIREFISH part 1, 21 participants were enrolled (*11*). Eligibility criteria included clinical diagnosis of type 1 SMA and genetic diagnostic confirmation of 5q-SMA. Patients who had previously received nusinersen and/or who required invasive ventilation or tracheostomy were excluded. The age range of the participants at symptom onset was 28 days to 3 months. The median age at enrolment was 6.7 months. At month 12, 7/21 (33%) participants, all in the high-dose cohort that was selected for part 2 (0.2 mg/kg per day), were able to sit without support for ≥ 5 seconds.

In FIREFISH part 2, 41 participants aged between 1 and 7 months were enrolled (*12*, *13*). The eligibility criteria were the same as in the first part of the study. The median age at enrolment was 5.3 months. At baseline, no participants were able to sit without support, the median Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score was 22.0 and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0. After 12 months of treatment, 12/41 (29%) participants were able to sit without support for ≥ 5 seconds, 23/41 (56%) participants had a CHOP-INTED score of 40 or higher and 37/41 (90%) had an increase of at least 4 points from baseline in their CHOP-INTEND score. At month 12, 32/41 (78%) participants were classified as having a HINE-2 motor-milestone response. After 24 months of treatment, 18/41 (44%) participants were able to sit without support for at least 30 seconds. No participants could stand alone or walk alone after 24 months.

SUNFISH was a company-funded, multicentre, randomized, double-blind, placebo-controlled, phase II/III study to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of risdiplam in non-ambulant adult and paediatric participants with type 2 and type 3 SMA. It was divided in two parts, an exploratory dose-finding part (part 1) for 12 weeks and then a confirmatory part (part 2) for 24 months. The eligibility criteria included a confirmed diagnosis of 5q-SMA, the absence of previous or concomitant use of nusinersen and other criteria. The age group eligible for study was between 2 and 25 years.

SUNFISH part 1 enrolled 51 participants. The median age at screening was 7 years and 4/51 (8%) were aged ≥ 18 years (*14*). Most participants (73%) had type 2 SMA. The median age of symptom onset was 14 months. Participants achieved a mean increase of 2.7 points in the 32-item Motor Function Measure (MFM32) from baseline to month 24. Participants achieved a mean increase of 2.5 points in the Revised Upper Limb Module (RULM) score and an overall increase of 0.6 points in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score.

Greater improvements in motor function were observed in younger participants (2–11 years) than in older participants (12–25 years).

SUNFISH part 2 enrolled 180 participants, 128 (71%) with type 2 SMA and 52 (29%) with type 3 (*15*). At screening, 68 (38%) were aged 12 years or older. Participants achieved a mean increase change from baseline to month 12 in MFM32 total score of 1.36 points in the risdiplam group. Mean change from baseline to month 12 in RULM total score was of 1.61 points. In HFMSE total score, mean change after 12 months was of 0.95 points. The greatest improvements in the scores were observed in the youngest patients.

Comparisons of risdiplam with other medicines for SMA

No direct comparison studies between risdiplam and the other treatments for SMA have been conducted.

A 2024 study evaluated long-term comparative efficacy and safety of risdiplam and nusinersen in children with type 1 SMA using an indirect treatment comparison method and data from 58 children in FIREFISH and aggregate data from 81 children enrolled in the ENDEAR and SHINE clinical trials of nusinersen (*16*). The study was funded by the manufacturer of risdiplam The study reported that risdiplam was superior to nusinersen for overall survival (hazard ratio (HR) 0.22, 95% CI 0.04 to 0.47) and event-free survival (HR 0.19, 95% CI 0.07 to 0.35). Risdiplam treatment was also associated with greater likelihood of achieving HINE-2 motor milestones (HR 1.45, 95% CI 1.21 to 1.80) and achieving ≥ 4-point improvement on CHOP-INTEND (HR 2.86, 95% CI 2.18 to 4.48).

A 2023 systematic review and meta-analysis of six randomized controlled trials (728 participants) evaluated the efficacy and safety of risdiplam and nusinersen in the treatment of SMA (*17*). The majority (5/6) of the trials included participants with types 2–4 SMA. No comparisons between treatments were made. The study concluded that both nusinersen and risdiplam were effective in the treatment of SMA, showing clinical improvement in motor function as measured by HFMSE and RULM, and were similar in terms of adverse effects when compared with placebo.

A 2022 study conducted an indirect treatment comparison of risdiplam with nusinersen and onasemnogene abeparvovec in patients with SMA (*18*). The study evaluated Individual patient data from risdiplam trials in comparison with aggregated data from published studies of the other treatments. From indirect comparisons of risdiplam and nusinersen in patients with type 1 SMA, the study found improved survival and motor function favouring risdiplam. The authors were unable to draw conclusions on the comparisons of risdiplam and nusinersen in patients with type 2/3 SMA, and risdiplam and onasemnogene abeparvovec in Type 1 SMA due to substantial differences in study populations.

Summary of evidence: harms

From 24-month results of the RAINBOWFISH trial, no treatment related adverse events leading to study withdrawal or treatment discontinuation were reported (*9*). In addition, no deaths or treatment-related serious adverse events were reported. The most commonly reported adverse events were teething (42%) and gastroenteritis (38%). Most adverse events were not considered to be treatment-related and resolved over time.

In FIREFISH part 1, 202 adverse events were reported, including 24 serious adverse events (*11*). The most common adverse events were pyrexia (52%), upper respiratory tract infection (43%), cough (24%) and vomiting (24%). The most common serious adverse events were pneumonia (14%), viral respiratory tract infection (10%) and acute respiratory failure (10%). Four infants died of respiratory complications, mainly due to the neuromuscular respiratory failure caused by the disease.

In FIREFISH part 2, at a clinical cut-off date of 12 November 2020, 359 adverse events were reported, including 28/41 (68%) infants with serious adverse events (*12*). The most frequently reported adverse events occurring in five or more participants were upper respiratory tract infection (54%), pneumonia (46%) and pyrexia (44%). Fatal events were reported in three infants, considered unrelated to treatment and secondary to SMA-related respiratory complications.

In SUNFISH part 2, 789 adverse events in risdiplam-treated participants were reported, with 93% of participants experiencing at least one adverse event and 20% experiencing at least one serious adverse event (*15*). The most frequently reported adverse events were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%) and headache (20%). The most frequently reported serious adverse event was pneumonia (8%). Adverse events with an incidence of ≥ 5 percentage points higher in the risdiplam group than the placebo group were pyrexia, diarrhoea and rash. No fatal adverse events were reported.

Additional evidence

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WHO guidelines

WHO guidelines for treatment of SMA are not available.

Costs/cost–effectiveness

All three medicines available for the treatment of SMA currently have a high cost.

Risdiplam pricing varies considerably across countries, with list prices reported in the application ranging from 529 United States dollars (US$) per unit (60 mg/80 mL powder for oral liquid) in China to US$ 13 504 per unit in the United States of America.

The application described health technology assessment performed by agencies in Australia (*19*), Brazil (*20*,*21*), Canada (*22*), France (*23*), Ireland (*24*), Kingdom of the Netherlands (*25*), New Zealand (*26*), Portugal (*27*) and the United Kingdom of Great Britain and Northern Ireland (*28*). In most countries, risdiplam was associated with very high incremental cost–effectiveness ratios generally considered not to be cost-effective. In countries where risdiplam has been recommended for reimbursement, most agencies have recommended reimbursement subject to conditions such as (confidential) price reductions, rebates or managed access arrangements. Many countries limit reimbursement to treatment of patients with SMA types 1, 2 and 3 only.

Results from a modelled cost–effectiveness evaluation of risdiplam versus nusinersen in people with SMA type 1 in China was reported in abstract form in 2022 (*29*). The model evaluated 10-year costs and effectiveness from a Chinese health-care system perspective. Risdiplam-treated patients had higher life-year and quality-adjusted life year gains. Direct medical costs associated with risdiplam treatment were lower than those for nusinersen. The study therefore concluded that risdiplam was dominant over nusinersen in China. A similar cost–effectiveness analysis in France found risdiplam dominated nusinersen in patients with SMA types 1, 2 and 3 (*30*).

A 2024 systematic review aggregated data from 20 economic studies evaluating the cost–effectiveness of risdiplam, nusinersen, onasemnogene abeparvovec and best supportive therapy in the treatment of SMA types 1 and 2. The analyses found that none of the treatments were cost-effective compared with best support therapy care (*31*).

The application also highlighted budget impact analyses that have reported the possibility of risdiplam being a cost-saving intervention when compared with alternative treatments for SMA (*32*–*33*).

Availability

Risdiplam has market authorizations in more than 100 countries for the treatment of SMA in patients aged 2 months and older. Market approval has been filed in several other countries. In some of these countries, the label was extended to include patients younger than 2 months based on positive interim data from RAINBOWFISH. The United States Food and Drug Administration approval for a dispersible tablet formulation of risdiplam was announced in early 2025.

Generic brands of risdiplam are not currently available. Roche and PTC Therapeutics have numerous patents covering the medicine in around 120 countries. The applicant has asked the manufacturer for a voluntary licence to produce and sell a generic version of risdiplam, however, these requests have been declined.

Other considerations

In about 33 countries, SMA is now tested at birth through routine newborn screening programmes that identify the disease (*34*). The testing for SMA varies by country context. In the next few years, this number is expected to increase steadily, especially in countries where medicines targeting the disease are available (*35*).

Committee recommendations

The Expert Committee again acknowledged the considerable morbidity and mortality associated with spinal muscular atrophy and the public health relevance of effective treatments. Considering SMA as a rare disease, the Committee reaffirmed the importance of equity, and that the rarity of a condition must not preclude medicines for its treatment from being included on the Model Lists if they meet the selection criteria of essential medicines. There are currently no treatments for SMA included on the Model Lists.

The Committee noted the evidence presented in the application from the FIREFISH and SUNFISH trials in symptomatic patients with SMA was the same as that presented in the 2023 application, with no new data reported. As in 2023, the Committee noted that the available evidence in this population remains limited and uncertain. In terms of benefits, the Committee again noted that greater improvements in motor function were reported in younger children (< 5 years) than in older children, adolescents and adults.

The Committee considered that risdiplam shows the greatest efficacy in the treatment of presymptomatic infants with SMA. The Committee considered new evidence from the RAINBOWFISH trial in this population, which presented results at 24 months of treatment. Evidence in the previous application presented results at 12 months of treatment. The Committee noted the promising 24-month results which indicated favourable outcomes for sitting without support, standing alone and walking alone in treated infants, with most achieving age-appropriate motor milestones. Additionally, all treated infants were reported to maintain bulbar function and none required permanent ventilation. However, at the time of the Committee's consideration, these data had been reported only in a conference presentation and had not yet been evaluated by the clinical and scientific community and published in a peer-reviewed journal. As such, the internal and external validity of the results could not be fully assessed by the Expert Committee due to limited available information.

Based on these considerations, the Expert Committee did not recommend the inclusion of risdiplam on the EML and EMLc at this time.

However, the Committee requested that an application for risdiplam, focusing on a clearly defined population of presymptomatic infants with SMA and presenting updated, published results of the RAINBOWFISH trial be submitted

for consideration by the 2027 Expert Committee. The Committee considered that if the preliminary results of the 24-month follow-up of the RAINBOWFISH trial are confirmed, if the risk of bias associated with the trial is low and if no evidence emerges against the use of risdiplam in this population (e.g. serious safety concerns), then a positive recommendation to include risdiplam on the EMLc could be possible in 2027. Considering the current very high price of risdiplam, reports of patent challenges and compulsory licence cases currently ongoing in India which have strong potential to result in the availability of generics and lower prices, the Committee requested the next application provide an updated overview of price and availability of risdiplam in different settings. Recognizing also the importance of newborn screening to identify infants with presymptomatic SMA most likely to benefit from risdiplam treatment, information on the availability and implementation of newborn screening for SMA should also be included in the next application.

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5.1.1 Antiseizure medicines

Prednisolone – new indication – EMLc

Prednisolone	ATC code: H02AB06

Proposal

Extension of the indications for the listing prednisolone on the EMLc to include treatment of infantile epileptic spasms syndrome.

Applicant

Archana A. Patel, Harvard Medical School, Boston Children's Hospital, Boston, MA, United States of America

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application and expressed support for the inclusion of prednisolone on the EMLc for the new indication.

EML/EMLc

EML

Section

5.1.1 Antiseizure medications

Dose form(s) & strengths(s)

Oral liquid: 1 mg/mL

Tablet: 1 mg, 5 mg, 10 mg

Core/complementary

Core

Individual/square box listing

Individual

Prednisone is not considered equivalent to prednisolone in infantile epileptic spasms syndrome treatment because young infants cannot efficiently convert prednisone to prednisolone due to their immature HSD11B1 enzyme systems.

Background

Prednisolone for use in the treatment of infantile epileptic spasms syndrome has not previously been evaluated for inclusion on the EMLc. Prednisolone for other

indications (e.g. allergy, hypersensitivity, oncology) has been included on the EMLc since the first list was published in 2007.

First-line treatment options for infantile epileptic spasms syndrome include hormonal treatment with oral prednisolone or adrenocorticotrophic hormone and non-hormonal treatment with vigabatrin (1–3). Neither adrenocorticotrophic hormone nor vigabatrin are currently included on the EMLc.

Public health relevance

Infantile epileptic spasms syndrome, previously known as West syndrome, affects about 30 per 100 000 live births annually, accounting for about 10% of epilepsies in children younger than 3 years (4, 5). It is characterized by brief tonic contractions of axial muscles which typically occur in clusters, developmental regression and a hallmark electroencephalogram pattern known as hypsarrhythmia showing chaotic, high-amplitude, excessive slowing and multifocal epileptiform discharges (4). It typically presents between 1 and 24 months of age, with a peak incidence between 3 and 12 months. Both sexes are affected, with a slightly higher incidence in males.

The condition is associated with an underlying epileptic encephalopathy that results in developmental slowing, arrest or regression, which usually begins or worsens at the onset of spasms (6). Without treatment, the long-term developmental and cognitive outcomes can be severe (4). Most children with infantile epileptic spasms syndrome have poor outcomes, with about 75% experiencing long-term cognitive deficits and 66% experiencing ongoing seizures (6). Delays in treatment initiation are associated with lower likelihood of clinical response, worse developmental outcomes and worse epilepsy outcomes (6, 7). If left untreated, mortality can exceed 30% (8).

Summary of evidence: benefits

A 2022 systematic review and network meta-analysis of 17 randomized controlled trials (987 participants aged 2 months to 3 years) compared effectiveness estimates and rankings of non-surgical interventions for infantile epileptic spasms syndrome (9). The most commonly reported treatments were high-dose adrenocorticotrophic hormone (nine randomized controlled trials, 237 participants), high-dose prednisolone (seven randomized controlled trials, 316 participants), high-dose vigabatrin (six randomized controlled trials, 219 participants), low-dose adrenocorticotrophic hormone (four randomized controlled trials, 75 participants), and prednisone (two randomized controlled trials, 26 participants). The primary outcomes analysed were electroclinical and clinical remissions within 1 month of starting treatment.

Electroclinical remission was reported by 16 randomized controlled trials (17 treatment pairs). Results of a fixed-effect frequentist meta-analysis

showed that all treatments were superior to placebo except for prednisone and vigabatrin (low-dose and high-dose). Network risk difference (RD) estimates for prednisolone were −0.42 (95% confidence interval (CI) −0.78 to 0.18) (low-dose) and −0.59 (95% CI −0.78 to −0.31) (high-dose). No significant differences were seen between prednisolone and high-dose adrenocorticotrophic hormone (RD 0.25, 95% CI −0.08 to 0.59 (low-dose); RD 0.09, 95% CI −0.17 to 0.34 (high-dose). High-dose prednisolone was superior to both low- and high-dose vigabatrin. Network ranking indicated that high-dose adrenocorticotrophic hormone had the highest probability of being the best intervention, followed by methylprednisolone and low-dose adrenocorticotrophic hormone in combination with magnesium sulfate. High-dose prednisolone (with and without vitamin B6) ranked fourth and sixth, respectively; low-dose prednisolone ranked tenth (*9*).

Clinical remission was reported by 13 randomized controlled trials (14 treatment pairs). Results of a fixed-effect frequentist meta-analysis showed that low-dose adrenocorticotrophic hormone (with and without magnesium sulfate), high-dose adrenocorticotrophic hormone (with and without vitamin B6) and high-dose prednisolone (with and without vitamin B6) were superior to placebo. Network RD estimates for high-dose prednisolone were −0.53 (95% CI −0.82 to −0.23; without vitamin B6) and −0.52 (95% CI −0.90 to −0.14; with vitamin B6). High-dose prednisolone was superior to low-dose prednisolone (RD 0.27, 95% CI 0.03 to 0.50), prednisone (RD 0.48, 95% CI 0.05 to 0.91) and high-dose vigabatrin (RD 0.28, 95% CI 0.11 to 0.44). High-dose adrenocorticotrophic hormone was superior to low-dose prednisolone, but no significant difference was seen between high-dose adrenocorticotrophic hormone and high-dose prednisolone (with and without vitamin B6). Network ranking indicated that low-dose adrenocorticotrophic hormone in combination with magnesium sulfate had the highest probability of being the best intervention, followed by high-dose adrenocorticotrophic hormone and high-dose adrenocorticotrophic hormone in combination with vitamin B6. High-dose prednisolone (with and without vitamin B6) ranked sixth and fourth, respectively; low-dose prednisolone ranked ninth (*9*).

The application identified other systematic reviews and meta-analyses that provide evidence of no significant differences between adrenocorticotrophic hormone and oral corticosteroids (prednisone, prednisolone) for electroclinical and/or clinical response (*10*–*14*).

Of note, while vigabatrin was shown to be inferior to hormonal therapies, some studies indicate that it is superior to hormonal therapies in infantile spasms due to tuberous sclerosis complex (*15*–*17*).

Studies assessing long-term outcomes in children with infantile epileptic spasms syndrome treated with prednisolone/prednisone or adrenocorticotrophic hormone generally found developmental and neurological outcomes to be similar between treatment groups (*18*–*20*).

Summary of evidence: harms

Adverse effects associated with the use of prednisolone are well known and can be significant. Long-term use can be associated with hypothalamic–pituitary–adrenal axis suppression, increased risk of infection, effects on cardiovascular and renal function, gastrointestinal adverse effects, reduced bone density, cataracts and glaucoma. Treatment of infantile epileptic spasms syndrome with prednisolone is usually short-term (4–5 weeks).

A 2022 systematic review and meta-analysis of three randomized controlled trials (343 participants) compared the safety of prednisolone/prednisone and adrenocorticotrophic hormone for treatment of infantile epileptic spasms syndrome (*12*). Pooled data showed no significant differences between treatments for irritability (relative risk (RR) 0.79, 95% CI 0.57 to 1.10), increased appetite (RR 0.78, 95% CI 0.57 to 1.08), weight gain (RR 0.86, 95% CI 0.56 to 1.32) and gastrointestinal upset (RR 0.60, 95% CI 0.35 to 1.02).

Corticosteroid therapy, even short-term as proposed for infantile epileptic spasms syndrome, can complicate vaccination protocols. Live or live-attenuated vaccines are contraindicated during the regimen and for 2–3 months afterward due to the risk of infection. Response to killed vaccines may be diminished, particularly for individuals receiving high doses.

WHO guidelines

WHO guidelines for the treatment of infantile epileptic spasms syndrome are not currently available.

Hormonal therapy with prednisolone or adrenocorticotrophic hormone, with or without vigabatrin, is recommended as first-line treatment for non-tuberous sclerosis complex associated infantile epileptic spasms syndrome in various national and institutional guidelines.

Costs/cost–effectiveness

A 2020 study evaluated the cost–effectiveness of adrenocorticotrophic hormone versus oral corticosteroids in the first-line treatment of infantile epileptic spasms syndrome from a patient perspective (*14*). The study used cost data from the United States for a 14-day course of treatment: 100 464 United States dollars (US$) for adrenocorticotrophic hormone and US$ 210 for prednisolone. The base-case analysis reported incremental cost–effectiveness ratios of US$ 333 and about US$ 1.43 million per case of spasms resolved for prednisolone and adrenocorticotrophic hormone, respectively. Results were robust to multiple sensitivity analyses and different assumptions. The authors concluded prednisolone at 4–8 mg/kg a day to be more cost-effective than adrenocorticotrophic hormone under a wide range of assumptions.

A 2024 study in India assessed the societal financial burden linked to infantile epileptic spasms syndrome (*21*). For 92 children with infantile epileptic spasms syndrome enrolled between August 2022 and March 2023, median medication charges were 20 502 Indian rupees (₹) (US$ 251.80) and consultation charges were ₹2975 (US$ 36.50). The highest costs were due to medications. Median medication costs were ₹15 400 (US$ 172.50) for adrenocorticotrophic hormone, ₹3021 (US$ 55.40) for vigabatrin and ₹540 (US$ 6.60) for prednisolone. Median direct non-medical costs were ₹31 650 (US$ 388.40), and median indirect costs were ₹10 100 (US$ 124.07). The median loss of days due to hospital visits was 12.

The application reported the price of prednisolone 5 mg as US$ 0.06, US$ 0.01, US$ 0.02 and US$ 0.05 per tablet in Brazil, Ghana, Kenya and the Philippines, respectively. Costs per recommended treatment course were all below US$ 15.

Availability

Prednisolone has wide global market availability and is already included on many national medicines lists for other indications.

Other considerations

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Committee recommendations

The Expert Committee recognized the importance of effective treatment options for infantile epileptic spasms syndrome. The Committee noted that early diagnosis and prompt treatment are critical to improving long-term developmental and seizure outcomes. The Committee also noted the antiseizure medicines currently included on the EMLc are not recommended as first-line treatments for infantile epileptic spasms syndrome.

The Committee considered that the evidence presented in the application from systematic reviews and meta-analyses and randomized controlled trials supported the effectiveness and safety of high-dose prednisolone in the treatment of non-tuberous sclerosis complex associated infantile epileptic spasms syndrome. For infantile epileptic spasms syndrome secondary to tuberous sclerosis complex, the Committee noted that vigabatrin may be an alternative first-line treatment.

The Committee noted the advantages of prednisolone over alternative first-line treatments (adrenocorticotrophic hormone and vigabatrin) in terms of ease of oral administration (in comparison with adrenocorticotrophic hormone which is administered subcutaneously or intramuscularly), cost–effectiveness, cost and affordability, and availability. Thus, the Committee considered prednisolone to be a more feasible treatment option, particularly in resource-constrained settings.

The Expert Committee therefore recommended the inclusion of prednisolone on the core list of the EMLc for the new indication of treatment of infantile epileptic spasms syndrome.

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5.1.4 Medicines for cerebral palsy

Baclofen – addition – EML and EMLc

Baclofen	ATC code: M03BX01

Proposal

Addition of baclofen to the core list of the EML and EMLc for the treatment of spasticity in adults and children with cerebral palsy.

Applicant

International Cerebral Palsy Society

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application which expressed support for the inclusion of baclofen on the Model Lists for the proposed indication. It was the view of the technical department that including baclofen on the Model Lists would support countries in prioritizing its inclusion in national EMLs, standard treatment guidelines, health service packages and procurement plans, which may help to improve appropriate use, availability and affordability, especially in low- and middle-income countries.

EML/EMLc

EML and EMLc

Section

5.1.4 Medicines for cerebral palsy

Dose form(s) & strengths(s)

Intrathecal injection: 500 microgram/mL in ampoule

Oral liquid: 10 mg/5 mL

Tablet: 10 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Baclofen has not previously been evaluated for inclusion on the Model Lists.

Diazepam, included on the Model Lists for other indications, may be used in the treatment of spastic cerebral palsy.

Public health relevance

The overall birth prevalence of cerebral palsy is about 2 per 1000 live births (*1*). In 2019, the global prevalence of cerebral palsy was estimated at 50 million (*2*). Individuals with cerebral palsy may have varying degrees of neurological impairments such as weakness, sensory deficits, cognitive impairments, loss of selective motor control, incoordination and hypertonia including spasticity, dystonia, and choreoathetosis. These deficits can impair motor function and interfere with care, comfort and positioning (*3*). Hypertonia, or spasticity, can also lead to hip subluxation, torsional deformities, gait abnormalities, contractures, higher energy expenditure and pain (*4*,*5*). There is no cure for cerebral palsy but early diagnosis and intervention, coupled with regular treatment, can have a meaningful impact on an individual's overall function and quality of life.

The treatments that are available for hypertonia are able to minimize the long term impact of some of the neurological impairments and improve function (*3*). The goal of hypertonia or spasticity management is to improve function, not only to reduce muscle tone. Optimum and early management of spasticity can help achieve developmental milestones, improve function, prevent contractures, increase tolerance of braces, help with care, comfort and positioning, and improve weight gain velocity (*6*).

Summary of evidence: benefits

Intrathecal baclofen versus placebo

A 2024 systematic review and meta-analysis evaluated the effect of intrathecal baclofen therapy delivered via spinal implant on severe spasticity and motor function in patients with cerebral palsy (*7*). The review included 19 studies (343 participants) on severity of spasticity and six studies (117 participants) on motor function. Intrathecal baclofen therapy was associated with a significant reduction in spasticity levels, as measured using Ashworth Scale or Modified Ashworth Scale scores (pooled standardized mean difference (SMD) −1.70, 95% confidence interval (CI) −2.15 to −1.25; $P < 0.0001$). For motor function, as assessed using the Gross Motor Function Measure (GMFM), intrathecal baclofen therapy was associated with a small but significant improvement in GMFM scores (SMD 0.15, 95% CI 0.08 to 0.22; $P = 0.003$). The authors reported that asymmetrical funnel plots and Egger tests indicated the presence of publication bias among the included studies.

A 2015 Cochrane systematic review of six studies (95 participants) evaluated intrathecal baclofen for the treatment of spasticity in children 0 to 18 years with cerebral palsy (8). One study did not report sufficient results to determine the effect of intrathecal baclofen compared with placebo. Of the remaining five studies, four used lumbar puncture or another short-term administration method to deliver intrathecal baclofen, and one used implantable baclofen pumps over 6 months. The data obtained were unsuitable for meta-analysis, so a qualitative summary was presented. The review reported that the results of all included studies suggested a beneficial effect of intrathecal baclofen in reducing spasticity in children with cerebral palsy. Reported outcomes included: a significant difference in muscle tone in lower extremities (but not upper extremities) between baclofen and placebo; significant differences in mean Ashworth Scale scores in the lower limbs between baclofen and placebo 4 hours post-injection; small but statistically significant changes in Ashworth Scale score in the upper limbs at time points up to 8 hours post-injection; decreased Ashworth Scale scores from baseline at time points up to 6 hours post-injection for all muscle groups except hip flexors at 2 hours post-injection; significantly reduced spasticity in four of 22 muscle groups assessed compared with control at 6 months; and positive differences in gross motor function scores favouring baclofen. The authors noted that the validity of the evidence was limited by the small sample sizes and methodological issues (including high or unclear risk of bias) in the studies. The authors concluded that there was limited short-term evidence of the effectiveness of intrathecal baclofen in reducing spasticity in children with cerebral palsy; however, the effect of treatment on long-term outcomes is uncertain.

Intrathecal baclofen versus other therapies

A 2020 systematic review of 47 studies investigated the use of intrathecal baclofen pump therapy for treatment of spasticity in cerebral palsy (14 studies, 312 participants) compared with selective dorsal rhizotomy – a surgical procedure that involves severing the lumbosacral sensory nerves in the spine to relieve pain (28 studies, 1016 participants) – and extracorporeal shockwave therapy – delivery of therapeutic electric shocks of varying frequencies at different time intervals to relieve pain (8 studies, 251 participants) (9). Each treatment intervention was associated with improvements in spasticity, measured variously as changes in Modified Ashworth Scale and GMFM scores. However, the review did not include a meta-analysis, so direct comparisons between treatments could not be made. The authors concluded that intrathecal baclofen pump therapy was a less invasive treatment option that could be titrated to individual patient needs, while noting the disadvantage of long-term maintenance requirements. Selective dorsal rhizotomy offers an effective method for permanent spasticity relief in young patients, however, its implementation is limited as only a few centres globally are able to perform this treatment. Extracorporeal shockwave therapy offers relief of

spasticity with minimal invasiveness but is relatively new and further studies are needed to establish optimal frequencies and application sites.

Oral baclofen versus placebo

A 2015 systematic review of six randomized controlled trials (130 participants) evaluated the effectiveness of oral baclofen for treatment of spasticity in children and adolescents with cerebral palsy (*10*). The overall methodological quality of the included studies was low. The motor classification, baclofen dosage and outcome measures varied widely across studies. The authors found conflicting evidence for the effectiveness of oral baclofen in reducing muscle tone or improving motor function or level of activity and concluded that the data were insufficient to support or refute use of oral baclofen in children and adolescents with spastic cerebral palsy. The application included brief summaries of the findings of the included individual trials.

The application stated that oral baclofen is commonly used to predict or assess responsiveness to intrathecal baclofen therapy in individuals with spasticity due to cerebral palsy. This approach is often taken because intrathecal baclofen therapy requires an invasive surgical procedure, so assessing a patient's tolerance and responsiveness to baclofen can help clinicians gauge whether the patient may benefit from the intrathecal route.

Oral baclofen versus other therapies

Alternative oral therapies to baclofen include diazepam and tizanidine. The few studies comparing them suggest that baclofen is more efficacious than tizanidine and has fewer adverse side-effects than both alternatives. The studies are small and were mostly conducted in the immediate years after the approval of baclofen by the United States Food and Drug Administration. In addition, most of the studies focused on patients with multiple sclerosis and showed very little difference between oral therapies.

A 1985 double-blind crossover study compared oral baclofen and oral diazepam for spasticity reduction in 13 patients over a period of 19 weeks. Both medicines were associated with overall improvement, with no significant difference in preference for either treatment (*11*). A 1988 randomized double-blind crossover study compared baclofen and tizanidine for treatment of spasticity in 48 patients with multiple sclerosis. No statistically significant difference in efficacy was reported, however, efficacy was judged to be good or excellent by 24% of patients receiving tizanidine and 39% of patients receiving baclofen (*12*). More recently, a randomized, prospective follow-up study compared diazepam and oral baclofen in 67 children with cerebral palsy. For the outcome measure of change in mean Modified Ashworth Scale scores, no significant difference was found between treatment groups (*13*).

Summary of evidence: harms

Commonly reported adverse effects of oral baclofen include somnolence, confusion, ataxia, polyuria and headache. Adverse reactions can occur with sudden discontinuation of baclofen, such as hallucinations, seizures, increased muscle tone or, in rare cases, more severe complications. Therefore, it is generally recommended to taper the dosage gradually, unless a clinical situation necessitates otherwise.

In the 2024 systematic review of intrathecal baclofen versus placebo, 501 participants (including some without cerebral palsy) were evaluated for safety outcomes (*7*). Adverse events reported included 75 catheter or pump complications and 203 medical complications. Seizure-related adverse events were of particular concern, including six reports of new-onset seizures, and seven reports of increased seizure frequency. There were 33 reports of infections, including eight reports of meningitis. There were 16 reports of cerebrospinal fluid leaks associated with intrathecal baclofen therapy. The most commonly reported adverse events (75 cases) were delivery system complications (dislocations, malfunctions and disconnections).

In the 2015 systematic review of oral baclofen versus placebo, three of the studies did not show a significant difference in adverse effects between treatment groups, while two studies reported a higher rate of adverse effects in baclofen treated patients (sedation and reduced muscle tone) (*10*). The review also highlighted several disadvantages that limit the use of oral baclofen in children including: the large (> 90%) interindividual variability in oral absorption and elimination creating difficulties in determining the appropriate dosage in paediatric patients; poor blood–brain barrier penetration and a short half-life of 3–4 hours, necessitating repeated daily dosing; moderate systemic side-effects such as somnolence, confusion, polyuria, headache, weakness, memory deficits, orthostatic hypotension; and severe neurological side-effects such as sudden withdrawal syndrome, baclofen overdose and risk of seizures (*10*).

Neonates born to mothers taking baclofen regularly may experience mild withdrawal symptoms after birth, such as increased muscle tone or jitteriness. In these cases, a gradual dose reduction before delivery is often advised when feasible. If tapering is not possible, caregivers should monitor the newborn for any signs of withdrawal.

Some individuals with certain pre-existing conditions may need closer monitoring when using baclofen. Patients with a history of stroke may not experience significant improvement in spasticity and may have reduced tolerance for the drug. Patients with psychiatric conditions may experience a temporary increase in symptoms and benefit from closer supervision. In patients prone to autonomic dysreflexia, the presence of specific stimuli or sudden withdrawal of baclofen could potentially trigger an episode of autonomic dysreflexia, while individuals with epilepsy may experience some variability in seizure control (*10*).

In terms of musculoskeletal effects, baclofen may affect patients who rely on muscle spasticity to maintain posture or mobility. In such cases, dose adjustments can help balance therapeutic benefits with maintenance of functional stability. Additionally, some women using baclofen long-term have reported the development of ovarian cysts, although these typically resolve without intervention.

Intrathecal baclofen pump therapy also has risks associated with the surgical procedure required to place the pump, as well as the injections required to refill the pump.

Additional evidence

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WHO guidelines

The WHO package of interventions for rehabilitation outlines the most essential rehabilitation interventions for 20 health conditions that have high prevalence rates and high levels of associated disability, including for cerebral palsy. The package includes, among other things, oral muscle relaxants (benzodiazepines and baclofen) as pharmacological interventions for children, adolescents and adults with cerebral palsy (*14*). The package does not currently include intrathecal baclofen. Inclusion of the oral muscle relaxant interventions in the package was based on a review of clinical practice guidelines for rehabilitation in cerebral palsy. The United Kingdom National Institute for Health and Care Excellence (NICE) clinical guidelines for management of spasticity in people younger than 19 years with non-progressive brain disorders informed the inclusion of oral muscle relaxants in the package of interventions (*15*).

The NICE guidelines include the following recommendations (*16*).

- Consider oral diazepam or baclofen in children and young people if spasticity is contributing to one or more of the following: discomfort or pain; muscle spasms, for example, night-time muscle spasms; and functional disability. Diazepam is particularly useful if a rapid effect is desirable (e.g. in a pain crisis). Baclofen is particularly useful if a sustained long-term effect is desired, for example, to relieve continuous discomfort or to improve motor function (conditional recommendations, moderate-certainty evidence).
- Give oral diazepam treatment as a bedtime dose. If the response is unsatisfactory, consider increasing the dose or adding a daytime dose (conditional recommendation, moderate-certainty evidence).
- If oral diazepam is initially used because of its rapid onset of action, consider changing to oral baclofen if long-term treatment is indicated (conditional recommendations, moderate-certainty evidence).

- Start oral baclofen treatment with a low dose and increase the dose stepwise over about 4 weeks to achieve the optimum therapeutic effect (strong recommendation, low to moderate-certainty evidence).
- Consider treatment with continuous pump-administered intrathecal baclofen in children and young people with spasticity if, despite the use of non-invasive treatments, spasticity or dystonia are causing difficulties with any of the following: pain or muscle spasms; posture or function; and self-care (or ease of care by parents or carers).

The NICE guidelines for cerebral palsy in adults include recommendations to consider: (i) enteral baclofen as the first-line pharmacological treatment for adults with cerebral palsy and generalized spasticity causing functional impairment, pain or muscle spasm; and (ii) referring adults with cerebral palsy to a tone or spasticity management service offering continuous pump-administered intrathecal baclofen therapy, if they still have difficulties with spasticity despite enteral muscle relaxant treatment or botulinum toxin type A treatment (*17*).

Other international guidelines include various recommendations for the use of oral and/or intrathecal baclofen in patients with spastic cerebral palsy.

Costs/cost–effectiveness

A French study modelled the cost–effectiveness of intrathecal baclofen versus other conventional treatment options as first-line treatment for disabling spasticity caused by any neurological disease (*18*). The study found that intrathecal baclofen as first-line therapy was associated with a higher treatment success rate (defined as a combination of increased patient and care-giver satisfaction as assessed by goal attainment scaling, and at least 1-point decrease in the Ashworth score) than conventional medical management despite having the highest acquisition cost of antispastic treatments. Over a 2-year time horizon, intrathecal baclofen therapy was associated with lower total medical costs than conventional treatments and was considered the dominant strategy. Mean cost–effectiveness ratios per treatment success were 75 204 euros (€) for intrathecal baclofen therapy versus €148 822 for conventional treatment.

A Dutch study conducted a cost-effectiveness analysis of intrathecal baclofen therapy versus standard treatment in children with spastic cerebral palsy from the health-care perspective over a 1-year time horizon (*19*). Intrathecal baclofen therapy was more effective and more costly than standard treatment with an incremental cost per quality-adjusted life year (QALY) gained of €32 737 using the Dutch EuroQol-5D index and €28 273 using the United Kingdom's EuroQol-5D index. The authors concluded that given a willingness-to-pay threshold of €80 000, intrathecal baclofen therapy was a cost-effective intervention for certain children with spastic cerebral palsy.

A study in the United States of America assessed the cost–effectiveness of intrathecal baclofen in children with severe spasticity of cerebral origin who were unresponsive to less invasive treatments (e.g. oral medicines) relative to alternative medical and surgical therapy from a health-system perspective over a 5-year time horizon (*20*). Intrathecal baclofen was associated with increased treatment costs and an average gain of 1.2 QALYs compared with alternative treatments, resulting in an incremental cost–effectiveness ratio of 42 000 United States dollars (US$) per QALY, which is within the range considered acceptable as offering good value for money.

In addition to the cost of the medicine, intrathecal baclofen requires a surgical procedure to install the pump and regular interventions to refill and maintain the pump, as well as further surgical procedures to replace the pump every 5–8 years. However, the additional cost and the need for surgical expertise mean that intrathecal baclofen is not available in many low- and middle-income countries.

No information on the cost of intrathecal baclofen ampoules was presented in the application.

Oral baclofen is widely available globally, including in generic forms. The application stated that no recent studies were available on its cost–effectiveness compared with other treatments. The application presented a summary of comparative costs for baclofen 10 mg tablets in multiple countries, which ranged from US$ 0.07 per tablet (US$ 6.30 per month) in Nigeria to US$ 0.40 per tablet (US$ 36.00 per month) in Argentina and the United States.

No price information was presented in the application for baclofen oral liquid.

Availability

Baclofen tablets are widely available globally. The availability of the oral liquid and intrathecal injection formulations does not appear to be as widespread.

According to the WHO Global essential medicines dashboard (*21*), baclofen is currently included in the national EML of 46 countries. The dashboard does not differentiate between different dosage forms.

Other considerations

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Committee recommendations

The Expert Committee recognized the significant public health burden associated with cerebral palsy. Effective management of spasticity in people with cerebral palsy is essential to improve mobility, posture, comfort and quality of life, particularly in children. The Committee noted that baclofen is widely used

in clinical practice for this indication but had not previously been evaluated for inclusion on the Model Lists. No other pharmacological treatments for spasticity in cerebral palsy are currently included on the EML or EMLc.

The Committee reviewed evidence from multiple systematic reviews and clinical studies. Most of the available evidence focused on use in children and adolescents up to 18 years. For intrathecal baclofen, the Committee noted evidence of significant benefit in reducing spasticity. Improvements in motor function were more modest. However, the quality of evidence was generally low, with concerns about heterogeneity of effect sizes across studies and risk of bias. The Committee also noted the risks of harms associated with intrathecal therapy, including infections, seizures and device-related complications. Overall, the Committee considered intrathecal baclofen to have a favourable balance of benefits to harms in reducing spasticity, a critical outcome. The Committee also highlighted the importance of integrating pharmacological treatment with rehabilitation and supportive care.

For oral baclofen, the Committee noted the weakness of the available evidence with limited and inconsistent findings from small, methodologically flawed studies. However, the Committee recognized the important role of oral baclofen: in assessing responsiveness to treatment before surgical placement of an intrathecal pump; as a complementary therapy during the intrathecal dose titration when the pump is installed; as a supportive therapy when intrathecal therapy is discontinued; and to prevent and treat baclofen withdrawal, which can be severe and life-threatening.

The Committee considered cost–effectiveness analyses from high-income settings, which suggested that intrathecal baclofen may be cost-effective in selected patients despite high initial and maintenance costs. However, the need for neurosurgical expertise and long-term device management may limit feasibility in many low- and middle-income countries. Furthermore, anatomical constraints for pump placement in very young children may mean intrathecal use is unsuitable for this age group. Oral baclofen is more affordable and widely available in generic form, although no recent cost–effectiveness studies were identified.

Based on these considerations, the Expert Committee recommended the addition of intrathecal baclofen to the complementary list of the EML and EMLc for the treatment of spasticity associated with cerebral palsy based on evidence of a favourable balance of benefits to harms in reducing spasticity. The Committee also recommended addition of oral baclofen, recognizing its role in assessing suitability for intrathecal treatment, and dose titration and cessation. The Committee also considered that oral baclofen may be the only available and affordable option in some resource-constrained settings. Given the importance of specialist oversight in people receiving baclofen, the Committee considered that listing it on the complementary list, rather than the core list, was appropriate.

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5.1.5 Medicines for headache disorders

Carbamazepine – new indication – EML

Carbamazepine	ATC code: N03AF01

Proposal

Extension of the indications for the listing of carbamazepine on the EML to include treatment of adults with trigeminal neuralgia.

Applicant

WHO Brain Health Unit

WHO technical department

Department of Mental Health, Brain Health and Substance Use

EML/EMLc

EML

Section

5 Medicines for diseases of the nervous system

Dose form(s) & strengths(s)

Oral liquid: 100 mg/5 mL

Tablet (chewable): 100 mg, 200 mg

Tablet (scored): 100 mg, 200 mg, 400 mg

Capsule (extended-release): 100 mg, 200 mg, 300 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Carbamazepine has not previously been evaluated for inclusion on the EML for the treatment of trigeminal neuralgia. It is currently listed for use in the treatment of epilepsy and bipolar disorder. No alternative treatments for trigeminal neuralgia are currently included on the EML.

Public health relevance

Trigeminal neuralgia is a neuropathic pain disorder characterized by paroxysmal and recurrent episodes of severe, electric shock-like pain along the sensory distribution of the trigeminal nerve. The pain is brief (lasting from a few seconds to 2 minutes), typically unilateral and can be triggered by innocuous stimuli such as brushing teeth, chewing or speaking (*1*,*2*). The pathophysiology involves hyperexcitable neuronal states and central sensitization, often due to demyelination or compression of the trigeminal nerve. Diagnosis requires careful clinical evaluation and may involve magnetic resonance imaging to identify neurovascular compression or exclude secondary causes (*3*).

Trigeminal neuralgia can be classified based on etiology into three types: classical (associated with neurovascular compression of the trigeminal nerve root); secondary (resulting from an underlying neurological condition such as multiple sclerosis or space-occupying lesions); and idiopathic (where no cause is found).

Epidemiological data on the global burden of trigeminal neuralgia are limited. Available evidence estimates a lifetime prevalence of between 0.16% and 0.30%, with an annual incidence between four and 29 cases per 100 000 person-years (*4*,*5*). Trigeminal neuralgia is more commonly seen in women than in men, with a female-to-male ratio of 1.5:1. Incidence increases with age, commonly presenting between ages 53 and 57 years and peaking after age 60 years, where rates reach up to 20 cases per 100 000 person-years. Although relatively uncommon in individuals younger than 30 years, onset can occur anywhere from 24 to > 90 years (*2*,*4*,*5*).

Trigeminal neuralgia is a debilitating condition that significantly affects essential daily activities, including speaking, eating, drinking, and facial contact, leading to a marked reduction in quality of life. Its natural history varies significantly between individuals but the condition typically follows a chronic, episodic course characterized by periods of complete remission lasting weeks, months or even years between episodes. Over time, remissions often shorten and untreated trigeminal neuralgia can progress to persistent pain or more complex, refractory syndromes (*2*,*4*). Epidemiological studies have demonstrated a higher prevalence of anxiety and depression in affected individuals, along with an increased risk of suicide (*6*).

Summary of evidence: benefits

The applicants did a literature search of PubMed and the Cochrane Library to identify recent systematic reviews and meta-analyses on the treatment of trigeminal neuralgia. The search was limited to systematic reviews and meta-analyses published in the past 10 years, with full text, and in English. The search yielded six systematic reviews and meta-analyses (*7*–*12*). Quantitative meta-analysis was not feasible due to significant heterogeneity in the medicines

investigated, study methods and the outcome measures assessed. Qualitative analysis of these studies noted a lack of robust, high-quality data on the efficacy of treatments for trigeminal neuralgia, including carbamazepine. No studies included in the systematic reviews provided strong evidence, such as high-tier randomized controlled trials with rigorous design and sufficient sample sizes, to firmly establish the efficacy of carbamazepine for trigeminal neuralgia. Thus, the findings of the systematic reviews were not elaborated on in the application. The application stated that the absence of comprehensive, high-quality evidence highlights the need for further well-designed studies to strengthen the foundation for evidence-based treatment guidelines.

Since the recently published reviews provided low-quality evidence, existing guidelines on trigeminal neuralgia treatment were reviewed. Among these, the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines were examined in detail (*13*). These guidelines found no robust studies that met the inclusion criteria to inform recommendations. Nonetheless, the NICE guideline development group acknowledged the debilitating nature of trigeminal neuralgia, underscoring the need for treatment, and noted that most patients in the United Kingdom with trigeminal neuralgia were already using carbamazepine, which suggests that the medicine has some efficacy over no treatment. Despite the paucity of robust evidence, the guideline development group made a strong recommendation to offer carbamazepine as initial treatment for trigeminal neuralgia.

The NICE guideline and other guideline recommendations are based mainly on evidence from three randomized controlled trials from the 1960s (*14*–*16*). These trials compared carbamazepine to placebo in patients with trigeminal neuralgia and reported on its effectiveness in reducing the frequency and severity of pain. The first study was a randomized crossover study comparing carbamazepine and placebo in 70 adult participants with trigeminal neuralgia (*14*). Participants received carbamazepine and placebo alternately for 2 weeks at a time for a total of 8 weeks, beginning with either carbamazepine or placebo. The outcomes assessed were pain severity, number of paroxysms daily and effect on triggering mechanisms. Carbamazepine was associated with a significant improvement in severity of pain, number of paroxysms, disappearance of some triggers (eating and contact) and number of triggers becoming inactive. In the second study, 24 participants were randomized to receive carbamazepine or placebo for 3 months (*15*). All carbamazepine-treated patients experienced significant pain relief, with minimal or no response observed in the placebo group (definitive numbers were not provided). In the third study, 44 participants with trigeminal neuralgia were randomized to receive carbamazepine or placebo (*16*). After 4 years, 73% of carbamazepine-treated patients achieved a good or excellent clinical response, compared with 25% in the placebo group, with a number-needed-to-treat of 2.1.

A 2024 Cochrane systematic review of 10 randomized controlled trials (480 participants) evaluated the efficacy and adverse effects of carbamazepine in the treatment of chronic neuropathic pain (including trigeminal neuralgia) and fibromyalgia in adults (*17*). Overall, no study provided first- or second-tier evidence for efficacy outcomes, with all falling under third-tier due to poorly defined outcomes, incomplete reporting and small sample sizes. In a subgroup analysis of studies of trigeminal neuralgia, the risk ratio (RR) for the outcome of any pain improvement was 6.02 (95% confidence interval (CI) 2.82 to 12.85), favouring carbamazepine (two studies, 98 participants). The review concluded that carbamazepine was likely effective for neuropathic pain, albeit with limitations due to the low quality of evidence, highlighting that none of the trials included was longer than 4 weeks duration, had good reporting quality or investigated outcomes equivalent to substantial clinical benefit.

Given the severity of trigeminal neuralgia and the widespread recommendation for carbamazepine, it is unlikely (and arguably unethical) to conduct placebo-controlled studies for trigeminal neuralgia, suggesting high-quality placebo-controlled randomized controlled trials will remain scarce. Current research is now focused on finding alternative agents with comparable or superior efficacy to carbamazepine, although none has proven superior to date. Thus, despite limited evidence and reported side-effects, carbamazepine remains the recommended first-line treatment for trigeminal neuralgia, as adopted by other guidelines.

A 2001 randomized controlled trial compared carbamazepine and oxcarbazepine in 48 patients with trigeminal neuralgia (*18*). All patients receiving oxcarbazepine and 19 (95%) receiving carbamazepine obtained a greater than 50% reduction in the number of pain attacks. However, the duration of follow-up, sample size calculation, assessment of outcome and allocation procedure were unclear from the study. A 2021 retrospective, real-world study of 354 patients with trigeminal neuralgia found similar efficacy between oxcarbazepine and carbamazepine for the proportion of patients achieving at least 30% reduction in pain (*19*). The proportions of respondents among patients treated with oxcarbazepine and carbamazepine were 90.9% (median dose 900 mg) and 88.3% (median dose 800 mg).

A 2016 meta-analysis of 16 randomized controlled trials (1330 participants) evaluated the efficacy and safety of gabapentin compared with carbamazepine in the treatment of trigeminal neuralgia (*20*). All included trials were from China. After 4–10 weeks follow-up, response to treatment was similar between treatment groups as measured by the total effective rate (odds ratio (OR) 1.6, 95% CI 1.2 to 2·2; 14 studies, 1156 participants; low-quality evidence). This meta-analysis had multiple weaknesses, including different study designs, unclear sample size and allocation procedures, and absence of original studies in English.

Other pharmacological agents that have been compared to carbamazepine and found to be of similar or inferior efficacy include botulinum toxin A, eslicarbazepine, lamotrigine, pimozide, tizanidine and topiramate (7).

Studies on combination therapies have shown desirable effects, although no proper randomized trials are available. Notably, almost all combinations therapies involve carbamazepine (21–23). The evidence for these combination therapies is low. However, the reports of carbamazepine being included in almost all these reported combinations further supports the need to have carbamazepine as the first-line choice of treatment.

Summary of evidence: harms

Carbamazepine is frequently known to cause undesirable effects, limiting its optimal usage. Commonly reported side-effects include dizziness, drowsiness, nausea, ataxia and vomiting. These side-effects are usually dose-dependent and most people are able to tolerate them (24). Side-effects are more common in older people, necessitating careful monitoring and dose adjustments. From trigeminal neuralgia trials, side-effects reported that led to treatment interruption include central nervous system effects, hyponatraemia (19) and skin rash (14).

In the 2024 Cochrane systematic review, adverse events were common with carbamazepine, affecting 65% of carbamazepine users versus 27% with placebo. Adverse events reported in >10% of patients receiving carbamazepine included dizziness, giddiness, somnolence and unsteadiness. Furthermore, 3% of carbamazepine users withdrew due to adverse effects, compared with no placebo-treated patients (17).

From the retrospective, real-world study comparing carbamazepine and oxcarbazepine in patients with trigeminal neuralgia, the rate of side-effects was higher with carbamazepine than with oxcarbazepine (43.6% versus 30.3%; $P<0.0001$) (19).

Carbamazepine has mild anticholinergic effects and elderly patients may be at increased risk of delirium, urinary retention and constipation (24, 25).

A 2015 review evaluated the safety of pharmaceutical treatments for trigeminal neuralgia in elderly people (26). However, no specific trials conducted for the elderly population are available. The reported trials usually excluded people with comorbid illnesses or on other medications, thus excluding most elderly people. If side-effects of carbamazepine are unacceptable in an elderly patient, consideration could be given to using oxcarbazepine instead (27, 28).

Carbamazepine is a known teratogen and should only be used during pregnancy when the benefits outweigh the risk of congenital malformations (24).

Carbamazepine is a potent inducer of the cytochrome P450 (CYP450) enzyme system, leading to significant drug–drug interactions. This enzyme induction accelerates the metabolism of many medications, reducing their

efficacy. Common interactions occur with other antiseizure medications, such as lamotrigine, phenytoin and valproate, often necessitating dosage adjustments to maintain therapeutic levels. Anticoagulants such as warfarin and direct oral anticoagulants are also affected, increasing the risk of clot formation. Similarly, primidone, oral contraceptives, statins and certain antiretroviral agents may be strongly inhibited and become less effective (*29*).

Additional evidence

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WHO guidelines

WHO guidelines for trigeminal neuralgia are not currently available. Carbamazepine is recommended by the WHO Mental Health Gap Action Programme (mhGAP) guidelines for treatment of epilepsy and bipolar disorder (*30*).

The use of carbamazepine is recommended as a first-line treatment for trigeminal neuralgia by various clinical guidelines, including NICE (*13*), the European Academy of Neurology (*31*), South African Standard Treatment Guidelines (*32*), French Headache Society and French Neurosurgical Society (*33*), and the American Academy of Neurology–European Federation of Neurological Societies (*27*).

Costs/cost–effectiveness

The application stated that no data existed on the cost–effectiveness of carbamazepine in the treatment of trigeminal neuralgia.

The cost of treating trigeminal neuralgia with carbamazepine varies by region and health-care system, but as a generic medicine, carbamazepine is relatively affordable and widely available, even in low- and middle-income countries, where its long-standing use in epilepsy helps ensure continued access.

A summary of carbamazepine prices in selected low- and middle-income countries was presented in the application. Prices per 200 mg tablet ranged from 0.01 United States dollars (US$) in India to US$ 0.34 in South Africa.

Availability

Carbamazepine has wide regulatory approval and availability globally. It is currently included on the national EML of 134 countries worldwide.

Other considerations

Routine therapeutic monitoring of serum carbamazepine levels is not recommended and in vitro diagnostic testing for therapeutic drug monitoring of carbamazepine is not included in the WHO Essential Diagnostics List. However, certain individuals, particularly elderly patients, may require periodic

testing, including a full blood count (to monitor bone marrow suppression), liver function tests (due to carbamazepine's potential for hepatotoxicity and elevated liver enzymes), and kidney function tests (due to risk of hyponatraemia). In these cases, monitoring serum levels can be useful to help adjust dosages or discontinue treatment if the risk of toxicity is high.

Committee recommendations

The Expert Committee noted that no medicines are currently included on the Model Lists for the treatment of trigeminal neuralgia and acknowledged the substantial impact of the condition on affected individuals. The Committee noted that carbamazepine has been routinely used in the treatment of trigeminal neuralgia for decades and is considered the standard of care in clinical practice.

The Committee reviewed the evidence presented in the application and noted that while carbamazepine is widely used in clinical practice and recommended in several national and international guidelines as a first-line treatment for trigeminal neuralgia, high-quality clinical evidence for its use is lacking. The available data are largely derived from small, older trials, and recent systematic reviews have not identified high-quality randomized controlled trials to substantiate its efficacy. The Committee therefore considered that the quality of the available evidence was inadequate and therefore confidence in the reported benefits and harms was limited.

Therefore, the Expert Committee did not recommend the inclusion of carbamazepine on the EML for the new indication of trigeminal neuralgia as the quality of the evidence did not meet the standard required for EML decision-making.

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Eletriptan and naproxen – addition – EML

Eletriptan	**ATC code: N02CC06**
Naproxen	**ATC code: M01AE02**

Proposal

1. Addition of eletriptan to the core list of the EML for acute treatment of migraine in adults as a therapeutic alternative to sumatriptan.
2. Addition of naproxen to the core list of the EML for acute treatment of migraine in adults.

Applicant

International Headache Society; European Headache Federation; Lifting the Burden; and Disease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application and highlighted the need for more treatment options for migraine attacks. The technical department advised that increasing accessibility to medicines for migraine was an important action to help reduce the disease's burden.

EML/EMLc

EML

Section

5.1.5.1 Medicines for acute migraine attacks

Dose form(s) & strengths(s)

Eletriptan

Tablet: 40 mg

Naproxen

Tablet: 500 mg

Core/complementary

Core

Individual/square box listing

Eletriptan: therapeutic alternative under the existing listing for sumatriptan

Naproxen: individual

Background

Eletriptan and naproxen have not previously been considered by the Expert Committee for inclusion on the EML for the acute treatment of migraine.

In 2021, following consideration of an application for the inclusion of sumatriptan on the EML for acute treatment of migraine, the Expert Committee recommended its addition to the core list of the EML. The Committee noted that in comparison with other triptans, for the outcome of pain freedom at 2 hours, the efficacy of sumatriptan was comparable to other triptans, with the exception of eletriptan 40 mg and 80 mg, which showed significantly better efficacy than sumatriptan 50 mg and 100 mg. Eletriptan was also superior to sumatriptan for outcomes of headache relief at 2 and 24 hours, less use of rescue medications and relief of migraine-associated symptoms. Although the Committee thought benefits were likely across the pharmacological class, few data were available on the efficacy, safety, price and availability of other triptans. The Committee therefore did not recommend the addition of alternative triptans at the time but indicated that it would consider requests for listing in future (*1*).

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise and odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (*2*). In about 25% of people affected, episodes may be preceded by transient focal neurological symptoms – most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits. The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide) and it is 2–3 times higher in women than men (*3*).

According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (*4*). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (*5*).

About 2–3% of people with episodic migraine (headache on fewer than 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month most of which have symptoms of migraine) (*6*). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (*7*).

Summary of evidence: benefits

The application presented the results of a systematic literature review and meta-analysis conducted by the applicants for the purpose of the application. For the

analysis of efficacy, the outcome measures were pain freedom at 2 hours from intake of medication and pain relief at 2 hours from intake.

Eletriptan versus placebo

Based on a meta-analysis by the applicants of 119 randomized controlled trials of the efficacy of triptans in the treatment of acute migraine, high-quality evidence was found to exist to recommend the use of eletriptan 20 mg and 40 mg for the acute treatment of migraine attacks. Evidence also supported the use oral almotriptan 12.5 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg, rizatriptan 5 mg and 10 mg, sumatriptan 50 mg and 100 mg and zolmitriptan 2.5 mg, and subcutaneous sumatriptan 6 mg. Additionally, moderate quality evidence existed to recommend oral naratriptan 1 mg and sumatriptan nasal spray 10 mg and 20 mg. The results of this meta-analysis were not included in the application.

Eletriptan versus other triptans

In comparative randomized controlled trials, for the outcome of pain freedom at 2 hours, eletriptan 40 mg was significantly more effective than sumatriptan 100 mg (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.20 to 2.40; three randomized controlled trials, 2257 participants (*8*–*10*)), and naratriptan 2.5 mg (RR 1.93, 95% CI 1.36 to 2.75; one randomized controlled trial, 391 participants (*11*)). While estimates of effect favoured eletriptan 40 mg, there were no significant differences with rizatriptan 10 mg, (RR 1.30, 95% CI 0.89 to 1.89; one randomized controlled trial, 53 participants (*12*)), or zolmitriptan 2.5 mg (RR 1.22, 95% CI 0.97 to 1.53, one randomized controlled trial, 735 participants (*13*)). Similarly, for the outcome of pain relief at 2 hours, eletriptan was more effective than sumatriptan 100 mg (RR 1.16, 95% CI 1.08 to 1.23), naratriptan 2.5 mg (RR 1.33, 95% CI 1.09 to 1.64) and rizatriptan (RR 1.40, 95% CI 1.02 to 1.94). No significant difference was found between eletriptan 40 mg and zolmitriptan 2.5 mg (RR 1.07, 95% CI 0.96 to 1.20; one randomized controlled trial).

A 2024 systematic review and network meta-analysis of 137 randomized controlled trials (89 445 participants) evaluated the comparative effects of 17 pharmacological interventions for treatment of acute migraine (*14*). In head-to-head comparisons, for pain freedom at 2 hours, there was very-low-certainty evidence that eletriptan was associated with significant benefit compared with naratriptan (odds ratio (OR) 3.01, 95% CI 2.13 to 4.25), sumatriptan (OR 1.46, 95% CI 1.18 to 1.81), and zolmitriptan (OR 1.52, 95% CI 1.17 to 1.97). For sustained pain freedom from 2 to 24 hours, eletriptan was also significantly more effective than naratriptan (OR 2.73, 95% CI 1.35 to 5.52), sumatriptan (OR 1.41, 95% CI 1.02 to 1.93) and zolmitriptan (OR 1.47, 95% CI 1.03 to 2.11) (low- or very-low-certainty evidence).

Naproxen versus placebo

Three randomized controlled trials (2179 participants) compared oral naproxen versus placebo for the treatment of acute migraine (15–17). For pain freedom at 2 hours, the pooled analysis showed benefits of naproxen 500 mg (RR 1.92, 95% CI 1.32 to 2.77) and 825 mg (RR 3.72, 95% CI 1.78 to 7.75) over placebo. For pain relief at 2 hours, both strengths of naproxen were associated with benefit compared with placebo (500 mg: RR 1.58, 95% CI 1.40 to 1.78; 825 mg: RR 1.61, 95% CI 1.16 to 2.22). The overall risk of bias was unclear and the quality of evidence very low.

Naproxen versus sumatriptan

One randomized controlled trial (88 participants) compared oral naproxen 500 mg versus oral sumatriptan 100 mg (18). No significant difference was found between treatments for pain freedom at 2 hours (RR 1.20, 95% CI 0.61 to 2.37). The risk of bias was unclear and the quality of evidence low.

Two randomized controlled trials (1917 participants) compared oral naproxen 500 mg with oral sumatriptan 50 mg or 85 mg (15, 16). Overall, the quality of evidence was low that 85 mg sumatriptan was superior to naproxen 500 mg for pain freedom at 2 hours (RR 1.51, 95% CI 1.22 to 1.88) and pain relief at 2 hours (RR 1.21, 95% CI 1.08 to 1.35). No significant difference was seen between naproxen 500 mg and sumatriptan 50 mg for either outcome measure. The risk of bias was unclear and the quality of evidence very low.

Naproxen versus other non-steroidal anti-inflammatory drugs

No head-to-head randomized controlled trials were identified that assessed the efficacy of naproxen versus aspirin, paracetamol, ibuprofen or other non-steroidal anti-inflammatory drugs. Indirect evidence was derived by the applicants from a recent systematic review and meta-analysis, which reported a pain-free rate at 2 hours of 22% for naproxen, 23% for acetyl salicylic acid, 20% for ibuprofen and 19% for paracetamol. Pain response at 2 hours was achieved in 44% of participants with naproxen, 42% with acetyl salicylic acid, 43% with ibuprofen and 46% with paracetamol (14).

Naproxen in combination with sumatriptan

Seven randomized controlled trials evaluated combination treatment with naproxen 500 mg and sumatriptan 50 mg or 85 mg versus placebo (15, 16, 19–23).

Meta-analysis of four randomized controlled trials (2728 participants) showed benefit associated with combination treatment with naproxen and sumatriptan 85 mg for pain freedom at 2 hours (RR 2.97, 95% CI 2.55 to 3.46) (19–22). More limited evidence from two randomized controlled trials (1811

participants) showed no significant difference between treatments for pain response at 2 hours (RR 1.54, 95% CI 0.78 to 3.03) (*15*, *22*). In each analysis, the quality of evidence was low.

One randomized controlled trial (491 participants) showed benefit associated with combination treatment with naproxen and sumatriptan 50 mg over placebo for pain freedom at 2 hours (RR 5.85, 95% CI 3.42 to 10.01) and pain relief at 2 hours (RR 2.42, 95% CI 1.93 to 3.03) (*16*). Meta-analysis of the remaining two randomized controlled trials showed benefits of combination treatment with naproxen and sumatriptan 85 mg for pain freedom at 2 hours (RR 2.73, 95% CI 1.85 to 4.04 and pain relief at 2 hours (RR 2.16, 95% CI 1.90 to 2.46) (*15*, *23*). The overall risk of bias of these trials was unclear and the quality of evidence was very low.

Summary of evidence: harms

A 2017 systematic review and network meta-analysis of 141 randomized controlled trials evaluated the comparative tolerability of 15 oral treatments for acute migraine (*24*). Among the triptan class, eletriptan, rizatriptan, sumatriptan, sumatriptan in combination with naproxen, and zolmitriptan were associated with significantly increased odds of any adverse event or treatment-related adverse events compared with placebo. With the exception of naratriptan, there was no significant increase in the odds of serious adverse events. No significant differences were reported between naproxen and placebo for any, treatment-related or serious adverse events. Results of selected comparisons are shown in Table 6.

Table 6
Network meta-analysis for adverse event outcomes from oral treatments for acute migraine

Comparison with placebo	Adverse event, odds ratio (95% credible interval)		
	Any	Treatment-related	Serious
Sumatriptan	**1.79 (1.57 to 2.05)**	**2.23 (1.83 to 2.73)**	2.20 (0.73 to 6.33)
Eletriptan	1.33 (0.95 to 1.81)	**1.95 (1.45 to 2.68)**	1.24 (0.23 to 5.30)
Naratriptan	1.11 (0.84 to 1.43)	0.86 (0.51 to 1.55)	**11.84 (1.25 to 106.10)**
Rizatriptan	**1.80 (1.54 to 2.12)**	**1.93 (1.51 to 2.45)**	1.66 (0.50 to 4.97)
Zolmitriptan	**2.22 (1.82 to 2.72)**	**1.75 (1.18 to 2.58)**	1.49 (0.47 to 4.31)
Sumatriptan + naproxen	**1.77 (1.34 to 2.30)**	**2.44 (1.66 to 3.59)**	0.10 (0.00 to 1.30)
Acetaminophen	1.33 (0.98 to 1.84)	**1.48 (1.05 to 2.11)**	1.28 (0.06 to 13.40)

Table 6 *continued*

Comparison with placebo	Adverse event, odds ratio (95% credible interval)		
	Any	Treatment-related	Serious
Ibuprofen	0.75 (0.36 to 1.59)	Not reported	Not reported
Naproxen	0.95 (0.69 to 1.33)	1.07 (0.72 to 1.58)	0.77 (0.02 to 10.34)

Statistically significant results are in bold.
Source: Thorlund et al; 2017 (*24*).

A 2016 systematic review and network meta-analysis of 88 randomized controlled trials compared the relative efficacy and tolerability of non-steroidal anti-inflammatory drugs and triptans for the treatment of migraine (*25*). The results suggested that eletriptan offered the best efficacy and acceptable tolerability among the 10 medicines evaluated.

Triptans

The presence of 5HT1B receptors in the coronary arteries has given rise to concerns about the risk of triptan-induced coronary arterial narrowing, further supported by individual cases of acute myocardial infarction in close temporal relationship with triptan intake. However, the incidence of triptan-induced serious cardiovascular adverse events in both clinical trials and clinical practice appears to be extremely low and limited to migraine patients with significant cardiovascular risks or with overt cardiovascular diseases. In line with these observations, analyses of reports of the United States Food and Drug Administration, observational studies and general practice research databases failed to reveal an increased risk of cardiovascular or cerebrovascular incidents in triptan users in the absence of vascular risk factors (*26*).

Triptans are associated with a statistically significant increase in odds of any adverse events or treatment-related adverse events compared with placebo, although they are usually mild to moderate in intensity, transient and resolve spontaneously. The most frequent adverse events include flushing, nausea, paresthesia and tingling.

Chest-related adverse events, characterized by chest pressure, chest pain, shortness of breath, palpitations and anxiety are not related to myocardial ischaemia according to aggregated data from trials, real-world experiences and pharmacodynamic instrumental assessments by electrocardiogram, myocardial scintigraphy and angiography. Therefore, these should be considered non-serious adverse events. Although rare, central nervous system adverse events (e.g. abnormal dreams, abnormal thinking, agitation, aphasia, asthenia, ataxia, confusion, dizziness, headache, somnolence, speech disorder, tremor, vertigo

and other focal neurological symptoms) may occur. The rates of incidence largely overlap among triptans with higher values for eletriptan 80 mg and lower values for almotriptan 12.5 mg.

The vasoconstrictive potential of triptans has led to the exclusion of patients older than 65 years with vascular diseases from phase III studies and thus they are not recommended for use in these patients. Nevertheless, several studies reported the use of triptans as safe in patients with stable vascular diseases, including people older than 65 years. Triptans are contraindicated in patients with coronary artery disease or coronary artery vasospasm, history of stroke, transient ischaemic attack, hemiplegic or basilar migraine, intracerebral or subarachnoid haemorrhage, hypertensive crisis, Wolff–Parkinson–White syndrome or other cardiac accessory conduction pathway disorders or arrhythmias, peripheral vascular disease, ischaemic bowel disease and severe hepatic impairment.

Naproxen

The application stated that no differences were detected in the trials assessed in this review between 500 mg naproxen and placebo (*24*). No difference was detected when comparing the combination naproxen and sumatriptan versus sumatriptan alone. The occurrence of adverse effects was lower in participants treated with naproxen alone compared with participants treated with a combination of naproxen and sumatriptan. No serious adverse events were reported in the available randomized controlled trials.

Additional evidence

A 2025 systematic review and network meta-analysis evaluating the benefits and harms of pharmacological treatments for acute episodic migraine attacks was identified during the review process (*27*). The review reported the combination a triptan and a non-steroidal anti-inflammatory drug had greater net benefit for outcomes of pain freedom at 2 hours and pain relief at 2 hours compared with triptan monotherapy (moderate-certainty evidence), a non-steroidal anti-inflammatory drug monotherapy (high-certainty evidence), paracetamol (low-certainty evidence) and newer, more costly therapeutic classes, such as a calcitonin gene-related peptide antagonists (low-certainty evidence).

WHO guidelines

WHO guidelines for the treatment of acute migraine are not currently available.

The application provided a brief summary of recommendations on the use of eletriptan and naproxen in acute migraine from various current national and international clinical guidelines.

Costs/cost–effectiveness

Eletriptan

The application noted that several studies have assessed the pharmacoeconomics of eletriptan, and were summarized in a manufacturer-funded review published in 2015 (*28*). This review reported "a consistent pattern [in which] eletriptan 40 mg, rizatriptan 10 mg and almotriptan 2.5 mg were shown to be more cost-effective than other triptans". This conclusion was based on costs at the time of publication of each included study, when generics were less widely available and pricing was less competitive.

The application described various cost analyses that were performed, the results of which are summarized in the following subsections.

Cost per treatment success

For the outcomes of pain freedom at 2 hours and headache relief, it was estimated that eletriptan 40 mg was, respectively, 13.2 times and 15.5 times more expensive than sumatriptan 100 mg.

Cost per healthy life year gained

For the outcomes of pain freedom at 2 hours and headache relief, the costs per healthy life year gained for eletriptan 40 mg were estimated at 10 971 United States dollars (US$) and US$ 5709, respectively.

Incremental cost–effectiveness for eletriptan 40 mg versus sumatriptan 100 mg

For the outcomes of pain freedom at 2 hours and headache relief, the costs per healthy life year gained for eletriptan 40 mg compared with sumatriptan 100 mg were estimated at US$ 37 993 and US$ 38 350, respectively.

Naproxen

No studies reporting the comparative cost or cost–effectiveness of naproxen in the treatment of acute migraine were identified in the application. Various cost analyses were performed as described in the application and the results are summarized in the following subsections.

Cost per treatment success

For the outcome of pain freedom at 2 hours, it was estimated that naproxen 500 mg was 4.2 times more expensive than ibuprofen 400 mg, and sumatriptan 100 mg was 3 times more expensive than naproxen 500 mg. For the outcome of headache relief, naproxen 500 mg was estimated to be 3.2 times more expensive than ibuprofen 400 mg, and sumatriptan was 3.5 times more expensive than naproxen 500 mg.

Cost per healthy life year gained

For the outcome of pain freedom at 2 hours, the cost per healthy life year gained for naproxen 500 mg was US$ 387 or US$ 1001 (depending on the price input used). For the outcome of headache relief, the cost per healthy life year gained for naproxen 500 mg was US$ 146 or US$ 387 (depending on the price input used).

Incremental cost–effectiveness for the combination of naproxen 500 mg and sumatriptan 50 mg versus sumatriptan 50 mg

The incremental cost–effectiveness ratio for naproxen plus sumatriptan compared with sumatriptan was calculated to be US$ 1026 per healthy life year gained.

Availability

A survey conducted among members of the International Headache Society reported naproxen was available in more than 70 countries globally, either as prescription or over-the-counter products. Multiple generic versions are available.

A survey conducted among members of the International Headache Society reported naproxen was available in more than 50 countries globally, as a prescription only product. Generic versions are available in a small number of countries.

Other considerations

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Committee recommendations

The Expert Committee noted that migraine is a common disabling primary headache disorder characterized by recurrent moderate to severe pain. It is a cause of disability and results in a substantial socioeconomic burden, which is greater for women than for men.

The Committee noted the very-low-quality evidence available on the efficacy of naproxen compared with placebo in terms of pain freedom and pain relief at 2 hours and the lack of head-to-head trials assessing the efficacy of naproxen versus aspirin or paracetamol (the currently available alternatives on the EML for this condition), or other non-steroidal anti-inflammatory drugs. However, indirect evidence reported similar rates of pain freedom at 2 hours. The Committee also noted that two randomized controlled trials showed no difference between naproxen and sumatriptan for the outcome of pain freedom at 2 hours (low and very low quality of evidence), while one showed that the 85 mg dose of oral sumatriptan was superior to oral naproxen 500 mg.

The Committee noted that a recent network meta-analysis reported the combination of oral sumatriptan and naproxen had the greatest net benefit compared with monotherapy with a triptan (moderate-certainty evidence), a non-

steroidal anti-inflammatory drug (high-certainty evidence), paracetamol (low-certainty evidence) or newer, more costly therapeutic classes, such as a calcitonin gene-related peptide antagonists (gepant, low-certainty evidence). Naproxen is generally well tolerated, with adverse effects rarely leading to discontinuation of treatment, and it is available in most countries at a reasonable price.

The Committee noted that naproxen has a different pharmacokinetic profile compared with other non-steroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen), with a longer half life and duration of action, which may be preferable for some patients.

Based on these considerations, and in recognition of the importance for people with migraine to have a range of treatment options available to them, the Expert Committee recommended the addition of naproxen to the core list of the EML for adults with acute migraine as a therapeutic alternative under a square box listing for ibuprofen.

The Committee recalled the 2021 decision to recommend the addition of sumatriptan to the core list of the EML for the treatment of adult patients with acute migraine and the consideration that there were likely to be benefits across the pharmacological class, but few data were available on efficacy, safety, price and availability of other triptans. The Committee noted that eletriptan 40 mg and 80 mg showed significantly better efficacy than sumatriptan 50 mg and 100 mg for the outcome of pain freedom at 2 hours. Eletriptan was also superior to sumatriptan for outcomes of headache relief at 2 and 24 hours and relief of migraine-associated symptoms and required less use of rescue medications.

The Committee noted that eletriptan is more costly than sumatriptan which is available as generics in several countries, and that at its current price, eletriptan is not cost-effective by most thresholds when used as a first-line triptan. Therefore, the Committee noted therapies with triptans should start with the one that has the lowest acquisition cost and more costly options can be used in cases of treatment failure or severe side-effects.

In line with previous consideration of the Committee that it is important for people with migraine to have a range of treatment options available to them, particularly for those with suboptimal responses or who are at risk of specific adverse events from currently listed analgesics, the Expert Committee recommended the addition of eletriptan to the core list of the EML as an alternative treatment option to sumatriptan in adults with acute migraine.

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Ibuprofen – new indication – EML

Ibuprofen **ATC code: M01AE01**

Proposal

Inclusion of ibuprofen on the core list of the EML for acute treatment of migraine in adults.

Applicant

International Headache Society; European Headache Federation; Lifting the Burden; and Dis-ease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application and expressed support for the inclusion of ibuprofen on the EML as an additional treatment option for treatment of acute migraine in adults.

EML/EMLc

EML

Section

5.1.5.1 Medicines for acute migraine attacks

Dose form(s) & strengths(s)

Tablet: 200 mg, 400 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Ibuprofen is currently included on the EML for other indications but has not been previously evaluated for acute treatment of migraine in adults.

Ibuprofen for acute treatment of migraine in children was included on the first EMLc in 2007. The EMLc subcommittee considered the burden of disease of migraine in children and noted that management was similar to that in adults but that fewer medicines were approved for the treatment of migraine in children. The subcommittee noted that acetylsalicylic acid (aspirin) is not recommended

for use in children due to the risk of Reye syndrome. Paracetamol and ibuprofen have been shown to be effective for acute migraine attacks in children, however, only paracetamol was included on the EMLc at that time. The subcommittee thus endorsed the addition of ibuprofen to the EMLc for this indication (*1*).

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise and odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (*2*). In about 25% of people affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide), and it is 2–3 times higher in women than men (*3*).

According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (*4*). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (*5*).

About 2–3% of people with episodic migraine (headache on fewer than 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month most of which are with symptoms of migraine) (*6*). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (*7*).

Summary of evidence: benefits

The application presented a pooled analysis of six randomized controlled trials comparing 200 mg, 400 mg and 600 mg ibuprofen with placebo for the treatment of migraine (*8*–*13*). The outcome measure reported was pain freedom at 2 hours. Information on the literature search strategy, criteria for trial selection and assessment of bias, among others, was not included in the application.

All dosage strengths of ibuprofen were associated with significant benefit compared with placebo: 200 mg (risk ratio (RR) 1.95, 95% CI 1.36 to 2.81; two randomized controlled trials, 777 participants), 400 mg (RR 2.68, 95% CI 1.81 to 3.95; five randomized controlled trials, 1689 participants) and 600 mg (RR 2.19, 95% CI 1.37 to 3.51; one randomized controlled trial, 340 participants).

Two of the trials compared different dosages of ibuprofen for the same outcome (*8*, *10*). The pooled analysis found no difference in pain freedom at 2 hours between 200 mg and 400 mg of ibuprofen (RR 1.00, 95% CI 0.77 to 1.31; two randomized controlled trials, 828 participants) or 400 mg and 600 mg (RR 0.95, 95% CI 0.69 to 1.30; one randomized controlled trial, 389 participants).

A 2016 Cochrane systematic review of 27 randomized controlled trials (7630 participants) assessed the effects of different pharmacological interventions, including ibuprofen, for treatment of migraine versus placebo in children (< 12 years) and adolescents (12–17 years) (*14*). One of the included studies was a three-way crossover study which evaluated ibuprofen, zolmitriptan and placebo in 29 children and adolescents (mean age 13.9 years) (*15*). For the outcome of pain freedom at 2 hours, no significant difference was found between ibuprofen and placebo (RR 7.00, 95% CI 0.99 to 49.69), while for the outcome of headache relief at 2 hours, ibuprofen was associated with significant benefit over placebo (RR 2.50, 95% CI 1.02 to 6.10). No significant differences were found between treatment arms for secondary outcomes including use of rescue medication, headache recurrence, nausea or vomiting.

Summary of evidence: harms

Potential harms associated with ibuprofen are well known. These include gastrointestinal adverse events such as bleeding and intestinal ulcers (including bleeding and perforation). The risk of bleeding increases with age, *Helicobacter pylori* infection and in those with a history of bleeding and/or anticoagulant use.

About 0.5% of people using non-steroidal anti-inflammatory drugs are reported to have an upper gastrointestinal bleed annually, although these are typically associated with long-term/chronic use (*16*, *17*).

A 2002 randomized study compared the gastrointestinal tolerability of ibuprofen, paracetamol and acetylsalicylic acid for common pain indications in 8633 in adults (*18*). The percentage of participants experiencing at least one gastrointestinal adverse event were 11.5%, 13.1% and 18.5% for ibuprofen, paracetamol and acetylsalicylic acid, respectively. Significantly more participants receiving acetylsalicylic experienced gastrointestinal adverse events compared with ibuprofen, while no significant difference was observed between paracetamol and ibuprofen.

From the Cochrane systematic review in children and adolescents, no significant difference was observed between ibuprofen and placebo for adverse events (*14*).

A 2010 meta-analysis and qualitative review evaluated the safety of ibuprofen compared with paracetamol in adults and children using data from 66 studies (*19*). The combined odds ratio (OR) for the proportion of adults experiencing at least one adverse event favoured ibuprofen, although the difference was not statistically significant (OR 1.12, 95% CI 1.00 to 1.25). No significant difference in the incidence of adverse events was observed in children.

Ibuprofen is contraindicated in the third trimester of pregnancy because of the risk of premature closure of the ductus arteriosus. It is safe for use during the first trimester of pregnancy (*20*), and in breastfeeding mothers.

Additional evidence

The following evidence was identified during the review process.

A 2013 Cochrane systematic review of nine randomized controlled trials (4373 participants) evaluated the efficacy and tolerability of ibuprofen (alone or in combination with an antiemetic) compared with placebo and other active interventions in the acute treatment of migraine in adults (*21*).

For pain freedom at 2 hours, significant benefit compared with placebo was reported for ibuprofen 200 mg (RR 1.96, 95% CI 1.36 to 2.81; two randomized controlled trials, 777 participants) and 400 mg (RR 1.91, 95% CI 1.60 to 2.28; six randomized controlled trials, 2575 participants). Significant differences favouring ibuprofen 200 mg and 400 mg were also reported for headache relief at 1 hour, headache relief at 2 hours, and sustained headache relief at 24 hours. The quality of the evidence was moderate. Similar proportions of participants in each treatment group experienced adverse events, which were mostly mild and transient. The relative risk of any adverse event of ibuprofen compared to placebo was 0.85 (95% CI 0.67 to 1.08) for 200 mg and 0.97 (95% CI 0.82 to 1.15) for 400 mg (*21*).

WHO guidelines

WHO guidelines for the treatment of acute migraine are not currently available.

The application noted that most current national and international clinical guidelines for headache and migraine include ibuprofen among the recommended first-line treatment options.

Costs/cost–effectiveness

No economic studies were identified in the literature that evaluated the cost–effectiveness of ibuprofen for the treatment of migraine. Various cost analyses were done by the applicants as described in the application and the results are summarized in the following sections.

Cost per dose

The application estimated the cost per dose of ibuprofen 400 mg to be almost 3 times lower than the cost per dose of dispersible aspirin 900 mg, based on lowest costs derived from the drug tariff of United Kingdom's National Health System. This, coupled with evidence of similar benefit of ibuprofen and aspirin, led the applicants to conclude that ibuprofen is more cost-effective than aspirin. An incremental cost–effectiveness analysis was not done.

Cost per healthy life year gained

For the outcomes of pain freedom and headache relief, the costs per healthy life year gained for ibuprofen were estimated at 190.28 United States dollars (US$) and US$ 91.10, respectively.

Availability

Ibuprofen tablets have wide global regulatory approval for treatment of mild to moderate pain.

Other considerations

Ibuprofen is already included on the national essential medicines lists of many countries (*22*).

Committee recommendations

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men.

The Committee noted that the evidence presented in the application came from six randomized controlled trials that had uncertain risk of bias. The pooled analysis showed benefits of ibuprofen (200 mg, 400 mg, and 600 mg) over placebo for the outcome of pain freedom at 2 hours. The Committee also noted that ibuprofen may have some advantages over paracetamol in both children and adults. The safety profile of ibuprofen is well known and it is generally well tolerated.

The Committee noted ibuprofen is already included in the EMLc for the treatment of migraine acute attack and it is largely available across countries at a reasonable price.

Based on these considerations, the Expert Committee recommended the addition of ibuprofen to the core list of the EML for the treatment of acute migraine in adults based on evidence of a favourable balance of benefits to harms. Listing is recommended for ibuprofen with a square box, with naproxen, also recommended at this meeting, as a specified therapeutic alternative.

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Amitriptyline – new indication – EML

Amitriptyline **ATC code: N06AA09**

Proposal

Extension of the indications for the listing of amitriptyline on the EML to include migraine prophylaxis in adults.

Applicant

International Headache Society; European Headache Federation; Lifting the Burden; and Disease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department did not support the inclusion of amitriptyline on the EML for migraine prophylaxis, suggesting that more evidence with clearer outcomes and specific indications for use in particular populations should be required to be considered for inclusion on the EML.

EML/EMLc

EML

Section

5.1.5.2 Medicines for migraine prophylaxis

Dose form(s) & strengths(s)

Tablet: 25 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Amitriptyline has not previously been evaluated for inclusion on the EML for migraine prophylaxis. It is currently listed for use in the treatment of depression and other common symptoms in palliative care. Propranolol is currently included in the EML for migraine prophylaxis.

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (*1*). In around 25% of people affected, episodes may be preceded by transient focal neurological symptoms – most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits. The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide), and it is two to three times higher in women than men (*2*).

According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (*3*). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (*4*).

Around 2–3% of people with episodic migraine (headache on < 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month of which a majority are with symptoms of migraine) (*5*). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (*6*).

Summary of evidence: benefits

The application presented the results of a critical re-appraisal and meta-analysis of amitriptyline for migraine prophylaxis (*7*). Three studies were included that compared amitriptyline and placebo for migraine prophylaxis (*8*–*10*). For efficacy outcome, two trials reported a ≥ 50% reduction in monthly migraine and one trial reported 50% responder rates. Two of the three trials were rated at high risk of bias, due to missing data on outcomes and failure to describe the methods for allocation concealment. In a pooled analysis, there was moderate-certainty evidence that amitriptyline probably increases the proportion of patients who experience ≥ 50% reduction in monthly migraine days (risk ratio 1.60, 95% confidence interval (CI) 1.17 to 2.19; three randomized controlled trials, 389 participants). A subgroup analysis based on risk of bias of the included trials did not indicate a difference between the trials at low and high risk of bias.

One cross-over randomized controlled trial compared the efficacy of amitriptyline with propranolol and placebo for migraine prophylaxis in 30 patients over 40 weeks (*11*). The reported outcome measure was a headache score calculated by multiplying headache hours by pain severity. The arithmetic mean of weekly scores was calculated. Both amitriptyline and propranolol were significantly superior to placebo. No significant difference was observed between amitriptyline and propranolol. Of note, the superiority of amitriptyline over placebo did not correlate with significantly reduced test scores for depression.

Summary of evidence: harms

Adverse effects of amitriptyline are well known and include drowsiness and anticholinergic symptoms (e.g. dry mouth, urinary retention, constipation, tachycardia, blurred vision), weight gain, glaucoma, benign prostatic hypertrophy, and PQ and QT interval prolongation.

In the pooled analysis presented in the application, there was moderate-certainty evidence that amitriptyline probably increases the proportion of patients who discontinue treatment due to adverse events compared to placebo (risk difference 0.05, 95% CI 0.01 to 0.10; two randomized controlled trials, 507 participants) (*7*).

The cross-over trial comparing amitriptyline and propranolol did not report safety outcomes (*11*).

Additional evidence

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WHO guidelines

WHO guidelines for migraine are not currently available.

The application provided a brief summary of recommendations on amitriptyline for migraine prophylaxis from various current national and international clinical guidelines.

Costs/cost–effectiveness

A 2015 cost–effectiveness analysis investigated interventions for migraine in four low- and middle-income countries including prophylaxis with amitriptyline (*12*). A population model was run for two scenarios over a lifetime horizon. Scenario 1 reflected the natural history of migraine and scenario 2 represented the population-level impact of each intervention implemented for 10 years. The population included was aged between 18 and 65 years. It was assumed that prophylaxis was only offered to people with three or more migraine attacks per month. Amitriptyline was cheaper than topiramate and more cost-effective than propranolol. The combination of amitriptyline prophylaxis and acute management with acetylsalicylic acid was associated with costs per healthy life year gained of 1649 United States dollars (US$), US$ 1795, US$ 5264 and US$ 773 in China, India, Russian Federation and Zambia, respectively. Costs were lower when treatment was accompanied by consumer education and prescriber training: US$ 959, US$ 957, US$ 3059 and US$ 573 per healthy life year gained, respectively.

Using the same modelling framework as the above study, the applicants conducted a cost–effectiveness analysis of amitriptyline versus propranolol. The model assumed an amitriptyline dose of 25 mg daily for the first week, 50 mg

daily for the second week and 75 mg daily thereafter, and a propranolol dose of 160 mg daily. Costs per healthy life year gained were US$ 560 for amitriptyline and US$ 887 for propranolol. In this analysis, amitriptyline dominated propranolol (i.e. lower cost and more effective). However, the results are considered highly uncertain due to the poor quality of the efficacy data.

Availability

Amitriptyline is widely available globally in branded and generic forms. In some jurisdictions, its use in migraine prophylaxis is an off-label indication.

Other considerations

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Committee recommendations

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life.

The Expert Committee noted that several classes of medication are commonly used for migraine prophylaxis, including antidepressants, anticonvulsants, antihypertensives and calcitonin gene-related peptide (receptor) monoclonal antibodies. Currently, the Model Lists include only propranolol for migraine prophylaxis.

The Committee noted that there is moderate-certainty evidence that amitriptyline increases the proportion of people who experience a 50% or greater reduction in monthly migraine days. However, amitriptyline was also associated with a greater proportion of patients who discontinued treatment due to adverse events compared with placebo.

Furthermore, the Committee noted that very few data exist comparing the efficacy and safety of amitriptyline versus active comparators, e.g. propranolol, other beta-blockers or other prophylaxis interventions.

Based on these considerations, the Expert Committee did not recommend the inclusion of amitriptyline on the EML for use in migraine prophylaxis. In the absence of adequate evidence for comparative benefit and safety versus currently listed propranolol, the Expert Committee was unable to determine if amitriptyline has a favourable and meaningful balance of benefits to harms.

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Bisoprolol – new indication – EML

Bisoprolol **ATC code: C07AB07**

Proposal

Extension of the indications for the listing of bisoprolol on the core list of the EML to include migraine prophylaxis in adults as a therapeutic alternative to propranolol.

Applicant

International Headache Society; European Headache Federation; Lifting the Burden; and Disease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department acknowledged the limitations of the evidence presented in the application but advised that including bisoprolol as an alternative to propranolol on the EML could potentially support countries in prioritizing its inclusion in national policies and procurement plans, which may help to improve appropriate use, availability and affordability.

EML/EMLc

EML

Section

5.1.5.2 Migraine prophylaxis

Dose form(s) & strengths(s)

Tablets: 1.25 mg, 5 mg

Core/complementary

Core

Individual/square box listing

Therapeutic alternative under the existing listing for sumatriptan (i.e. add square box to sumatriptan)

Background

Bisoprolol has not previously been evaluated for inclusion on the EML for migraine prophylaxis. It is currently listed for use in the treatment of cardiovascular

conditions (angina, arrhythmias, hypertension and heart failure). Propranolol is currently included in the EML for migraine prophylaxis.

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise, odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (*1*). In around 25% of those affected, episodes may be preceded by transient focal neurological symptoms – most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits. The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide), and it is two to three times higher in women than men (*2*).

According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (*3*). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (*4*).

Around 2–3% of people with episodic migraine (headache on < 15 days/month) transition to more disabling chronic migraine (headache on ≥ 15 days/month of which a majority are with symptoms of migraine) (*5*). One of the main risk factors for the transition to chronic migraine is poorly managed acute treatment and the overuse of acute medications (*6*).

Summary of evidence: benefits

The applicants conducted a systematic literature review and meta-analysis of randomized controlled trials of beta-blockers in migraine prophylaxis. For the analysis of efficacy, the outcome measures considered were: persisting monthly headache/migraine days, defined as the residual days reported by patients at the end of treatment; change in monthly headache/migraine days, defined as the variation in days reported by patients from baseline to the end of follow-up; and responder rate, defined as the proportions of patients reporting a ≥ 50% reduction of monthly headache/migraine days or monthly attacks compared with baseline. The application presented the results for propranolol and bisoprolol, both versus placebo, only. No studies were identified that compared propranolol and bisoprolol.

Propranolol

Ten randomized controlled trials comparing propranolol with placebo for migraine prophylaxis were identified, eight of which did not report the predefined efficacy outcomes (*7*–*14*). Of the remaining two, one was a placebo-controlled trial which evaluated topiramate for prophylaxis in episodic migraine with propranolol as an active control arm (*15*). The other was a comparative study

of candesartan versus propranolol for migraine prophylaxis without distinction between episodic and chronic (*16*). In the randomized controlled trial in episodic migraine, for the outcome of change in monthly migraine days, there was low-certainty evidence that propranolol 160 mg was superior to placebo (standardized mean difference (SMD) −0.27, 95% confidence interval (CI) −0.51 to −0.04; one randomized controlled trial, 286 participants). For the outcome of ≥ 50% responder rate, there was low-certainty evidence that propranolol 160 mg was superior to placebo (risk ratio (RR) 1.97, 95% CI 1.37 to 2.83; one randomized controlled trial, 286 participants). In the randomized controlled trial without distinction between episodic and chronic migraine, there was moderate-certainty evidence of no significant difference between propranolol 160 mg and placebo for persisting monthly migraine days (SMD −0.31, 95% CI −0.67 to 0.05; one randomized controlled trials, 120 participants) or of ≥ 50% responder rate (RR 1.71, 95% CI 0.99 to 2.98; one randomized controlled trial, 120 participants).

From the remaining studies, there was low-certainty evidence of benefits of propranolol 80 mg (RR 2.17, 95% CI 1.06 to 4.42; one randomized controlled trial, 36 participants) and 160 mg (RR 2.00, 95% CI 1.37 to 2.92; one randomized controlled trial, 72 participants) over placebo for ≥ 50% responder rate, and of propranolol 160 mg over placebo for persisting monthly migraine attacks, however for this outcome, the difference was not significant (SMD −1.00, 95% CI −2.00 to 0.01; four randomized controlled trials, 334 participants).

Bisoprolol

One randomized controlled trial (152 participants) was identified comparing bisoprolol 5 mg or 10 mg with placebo as prophylaxis in patients with migraine without distinction between episodic and chronic (*17*). For the outcome of persisting monthly migraine days, there was very-low-certainty evidence for benefit of bisoprolol 5 mg (SMD −0.38, 95% CI −0.70 to −0.06) and bisoprolol 10 mg (SMD −0.36, 95% CI −0.68 to −0.04) over placebo. For the outcome of the change in monthly migraine days, there was very-low-certainty evidence for benefit of bisoprolol 5 mg and 10 mg (SMD 0.34, 95% CI 0.02 to 0.66).

Summary of evidence: harms

Adverse effects associated with beta-blockers are well known and can be significant. Effects vary within the class depending on the cardioselectivity of the medicines. Contraindications include use in people with asthma, congestive heart failure and depression.

From the randomized controlled trial comparing bisoprolol and placebo, the most frequently reported adverse events were fatigue and dizziness, with the difference between bisoprolol and placebo for dizziness being statistically significant. Heart rate, and systolic and diastolic blood pressure were significantly lower in the bisoprolol groups than in the placebo group (*17*).

Additional evidence

A 2019 systematic review and network meta-analysis of 158 randomized controlled trials evaluated the efficacy of beta-blockers in preventing migraine and tension-type headache (*18*). The results of the network meta-analysis found high-quality evidence that propranolol is better than placebo, but found no significant differences between beta-blockers (propranolol, bisoprolol, metoprolol, timolol and nadolol) for the outcomes of headache frequency at 8 weeks and 12 weeks.

WHO guidelines

WHO guidelines for migraine prophylaxis are not currently available.

The application provided a brief summary of recommendations on beta-blockers for migraine prophylaxis from various national and international guidelines.

Costs/cost–effectiveness

The application stated that no published studies existed on the cost–effectiveness of propranolol or bisoprolol for migraine prevention. The application and presented a new modelled cost–effectiveness assessment comparing bisoprolol 5 mg daily with propranolol 160 mg. Costs per healthy life year gained were 136 United States dollars (US$) for bisoprolol and US$ 417 for propranolol. Incremental cost–effectiveness modelling found propranolol to be dominated by bisoprolol. The analyses were sensitive to medicine costs. The application highlighted the wide uncertainties in the analyses due to the poor quality of the trial data used in the model.

Availability

Bisoprolol has wide global regulatory approval and market availability. Generics are available in most countries.

Other considerations

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Committee recommendations

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life.

The Committee noted that several classes of medication are commonly used for migraine prophylaxis, including antidepressants, anticonvulsants, antihypertensives and calcitonin gene-related peptide (receptor) monoclonal antibodies. Currently, the Model Lists include only propranolol for migraine prophylaxis.

The Committee noted that the only evidence for bisoprolol presented in the application was a single randomized controlled trial that compared oral bisoprolol 5 mg or 10 mg to placebo over a treatment period of 12 weeks in people with migraine and that this trial was at serious risk of bias. The trial showed a significant reduction in the frequency of migraine attacks but no effect on the duration and severity of the attacks. No studies comparing propranolol with bisoprolol are available.

The Committee accepted the known safety profile and contraindications of beta-blockers. Data on safety of propranolol and bisoprolol for the prophylaxis of migraine are limited, however no additional serious safety signals emerge.

The Committee noted that bisoprolol and propranolol differ in their pharmacokinetic properties (e.g. half-life, duration of action). the potential advantage of a reduced frequency of dosing with bisoprolol may be offset by a prolonged-release formulation of propranolol.

The Committee acknowledged that the benefit of beta blockers for episodic migraine seems to be a class effect, but that most data and the highest quality data are available for propranolol. The Committee considered that the data presented for bisoprolol were too limited and of inadequate quality to support EML listing.

Based on these considerations, the Expert Committee did not recommend the inclusion of bisoprolol on the EML as a therapeutic alternative to propranolol due to there being inadequate evidence for comparative benefit.

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Fremanezumab – addition – EML

Fremanezumab **ATC code: N02CD03**

Proposal

Addition of fremanezumab with a square box as representative of the pharmacological class of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies to the core list of the EML for preventive treatment of high-frequency and chronic migraine in adults.

Applicant

International Headache Society; European Headache Federation; Lifting the Burden; and Disease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application. The technical department noted that evidence from direct head-to-head comparisons with currently used oral migraine prophylaxis treatments was not presented in the application and highlighted the high cost of anti-CGRP monoclonal antibodies.

EML/EMLc

EML

Section

5.1.5.2 Medicines for migraine prophylaxis

Dose form(s) & strengths(s)

Injection (subcutaneous): 225 mg/1.5 mL in prefilled syringe

Core/complementary

Core

Individual/square box listing

Square box, with fremanezumab as the representative of the pharmacological class of anti-CGRP monoclonal antibodies. Proposed therapeutic alternatives were erenumab, eptinezumab and galcanezumab.

Fremanezumab was proposed as the representative agent for the following reasons:

- unlike eptinezumab, which is infused intravenously, fremanezumab is administered subcutaneously and is therefore suitable for self-administration at home;
- unlike galcanezumab and erenumab, which are marketed with an auto-injector device, fremanezumab is administered with a prefilled syringe, which is more cost-effective;
- unlike these alternatives, which are administered according to a single-dosing scheme (monthly or quarterly), fremanezumab has two dosing schemes (monthly and quarterly), the latter being more manageable in difficult environments to favour adherence and minimize the costs of refrigerated storage;
- evidence exists that fremanezumab causes fewer side-effects than the other anti-CGRP therapies, e.g. erenumab has been associated with a higher occurrence of constipation and some concerns exist that it may cause hypertension.

Background

Neither fremanezumab nor other anti-CGRP monoclonal antibodies have previously been evaluated for inclusion on the Model Lists.

The EML currently includes only propranolol (with a square box) for migraine prophylaxis.

Public health relevance

Migraine is a prevalent neurovascular disorder characterized by moderate to severe headache attacks, often accompanied by nausea, vomiting, photophobia/phonophobia and sensitivity to external stimuli (light, noise and odours). Symptoms are disabling and affect participation in life activities, quality of life and productivity (*1*). In about 25% of people affected, episodes may be preceded by transient focal neurological symptoms (most commonly visual disturbances, less commonly paresthesias, rarely motor or language deficits). The global prevalence of migraine is estimated at 14–15% (more than 1 billion people worldwide) and it is two to three times higher in women than men (*2*).

According to the Global Burden of Disease study 2021, migraine was the fourth highest cause of years lived with disability at level 4 (*3*). In an analysis of the Global Burden of Disease study 2016, migraine accounted for 45.1 million disability-adjusted life years (*4*).

Chronic migraine is defined as 15 or more headache days per month for at least 3 months (*5*). About 3% of the general population experiences chronic migraines and each year, 2–3% of people with episodic migraine (fewer than 15 headache days per month) transition to a chronic migraine state (*6*, *7*).

Summary of evidence: benefits

The application presented the results of a systematic literature review and meta-analysis conducted for the purpose of the application. For the analysis of efficacy, the outcome measures were: change in monthly headache/migraine days (defined as the variation in days reported by participants from baseline to the end of follow-up as reported in headache diaries); and ≥ 50% responder rate (defined as the proportion of participants reporting a ≥ 50% reduction in monthly headache/migraine days compared with baseline). The ≥ 50% reduction of monthly attacks was also considered for ≥ 50% responder rate when the reduction in monthly headache/migraine days was not available. Overall, 27 studies were included in the quantitative synthesis, of which eight assessed fremanezumab.

Episodic migraine

Four randomized controlled trials compared fremanezumab to placebo in patients with episodic migraine (*8*–*11*). For the outcome of change in monthly migraine days at 12 weeks, the pooled analysis showed benefits of fremanezumab 225 mg monthly (standardized mean difference (SMD) −0.56, 95% confidence interval (CI) −0.76 to −0.36) and fremanezumab 675 mg quarterly (SMD −0.56, 95% CI −0.86 to −0.26) over placebo. For the outcome of ≥ 50% responder rate, both dosages of fremanezumab were associated with benefit compared with placebo (225 mg: risk ratio (RR) 2.02, 95% CI 1.38 to 2.97; 675 mg: RR 2.07, 95% CI 1.32 to 3.26). In absolute terms, 256 more per 1000 (95% CI 95 more to 493 more) for 225 mg and 336 more per 1000 (95% CI 7 fewer to 1000 more) for 675 mg. The quality of evidence for both outcomes was high.

Chronic migraine

Four randomized controlled trials compared fremanezumab to placebo in patients with chronic migraine (*10*, *12*–*14*). Fremanezumab 225 mg monthly was associated with benefits over placebo for change in monthly migraine days (SMD −0.39, 95% CI −0.62 to −0.16) and ≥ 50% responder rate (RR 2.11, 95% CI 1.70 to 2.63). In absolute terms this means 199 more responders per 1000 (95% CI 135 more to 279 more). The quality of evidence for both outcomes was moderate, downgraded due to the use of a 675 mg loading dose that is not approved for clinical use. Fremanezumab 675 mg quarterly was associated with benefits over placebo for change in monthly migraine days (SMD −0.34, 95% CI −0.58 to −0.09), and ≥ 50% responder rate (RR 2.08, 95% CI 1.73 to 2.51). In absolute terms, 182 more per 1000 (95% CI 115 more to 267 more). The quality of evidence for both outcomes was high.

No evidence was presented in the application addressing the benefits of other anti-CGRP monoclonal antibodies.

Summary of evidence: harms

According to the European Medicines Agency's summary of product characteristics for fremanezumab, more than 2500 patients have been treated with fremanezumab in registration studies, representing more than 1900 patient-years of exposure. More than 1400 patients were treated for at least 12 months. The most commonly reported adverse drug reactions were local injection-site reactions: pain (24%), induration (17%), erythema (16%) and pruritus (2%). These events were reported to be transient, predominantly mild to moderate in severity and generally did not necessitate treatment discontinuation. Anaphylactic hypersensitivity reactions were reported rarely. In placebo-controlled studies, 6/1701 (0.4%) patients treated with fremanezumab developed anti-drug antibodies, one of whom who developed neutralizing antibodies. Antibody responses were of low titre. With 12 months of treatment, anti-drug antibodies were detected in 43/1888 (2.3%) patients with 0.95% of the patients developing neutralizing antibodies. The safety and efficacy of fremanezumab were not affected by development of anti-drug antibodies (*15*).

A 2023 systematic review of 19 randomized controlled trials (14 584 participants) compared the safety and tolerability of monoclonal antibodies targeting the calcitonin gene-related peptide pathway and small molecule gepants in migraine prevention (*16*). From the network meta-analysis, significantly greater odds of treatment-emergent adverse events were associated with fremanezumab 225 mg (odds ratio (OR) 1.21, 95% CI 1.02 to 1.42), fremanezumab 675 mg (OR 1.20, 95% CI 1.02 to 1.41), galcanezumab 120 mg (OR 1.40, 95% CI 1.16 to 1.70) and galcanezumab 240 mg (OR 1.63, 95% CI 1.33 to 2.00). No significant differences were found between anti-CGRP monoclonal antibodies and placebo for serious adverse events. Eptinezumab was associated with the lowest odds of treatment-emergent adverse events and serious adverse events compared with placebo. Erenumab was associated with the lowest odds of any adverse events. Both doses of erenumab and fremanezumab had the lowest odds of adverse events leading to treatment discontinuation.

A 2023 retrospective analysis evaluated adverse events associated with erenumab, fremanezumab and galcanezumab spontaneously reported to the adverse event reporting system of the United State Food and Drug Administration in the first 6 months of launching the medicines (*17*). The most commonly reported adverse events per 1000 exposed patients for erenumab were wrong technique, constipation and migraine. The most commonly reported adverse events per 1000 exposed patients for fremanezumab were headache, drug ineffectiveness and migraine. The most commonly reported adverse events per 1000 exposed patients for galcanezumab were injection-site pain, underdose and headache.

Additional evidence

A 2023 systematic review and network meta-analysis (74 randomized controlled trials, 32 990 participants) assessing the comparative effectiveness of different migraine preventive medicines was identified during the application review process (*18*). Medicine classes Included were antidepressants, antiepileptics, antihypertensives, anti-CGRP monoclonal antibodies, calcium channel blockers and gepants. Anti-CGRP monoclonal antibodies were found to be the most effective class for increasing the proportion of patients achieving a ≥ 50% reduction in monthly migraine days and reducing the number of monthly migraine days. Fremanezumab was the most effective within in its class for these outcomes. For adverse events leading to discontinuation, anti-CGRP monoclonal antibodies were not different compared with placebo.

WHO guidelines

WHO guidelines for the prevention of high frequency and chronic migraine are not currently available.

The application provided a brief summary of recommendations related to anti-CGRP monoclonal antibodies as preventive treatment for episodic or chronic migraine from various current national and international clinical guidelines.

Costs/cost–effectiveness

The application reported current wholesale prices provided by Teva Pharmaceuticals for frem-anezumab 225 mg injection as 102.05 euros (€) in Argentina and €786.27 in the United States of America.

A 2022 systematic review evaluated economic evaluations of pharmacological treatments for adults with chronic migraine (*19*). Sixteen model-based cost-utility studies were included which evaluated botulinum toxin ($n = 6$), erenumab ($n = 8$), fremanezumab ($n = 2$) and galcanezumab ($n = 1$) as the main treatment. Of the two studies evaluating fremanezumab, a United States study reported the incremental cost–effectiveness ratio for fremanezumab versus no preven-tative treatment to be 115 000 United States dollars (US$) per quality-adjusted life year (QALY), well above the baseline willingness-to-pay threshold of US$ 50 000/QALY. A evaluation by the United Kingdom's National Institute for Health and Care Excellence (NICE) reported incremental cost–effectiveness ratios for fremanezumab of 11 825 pounds sterling (£)/QALY versus best supportive care and £16 227/QALY versus botulinum toxin type A.

The NICE technology appraisal concluded that the most plausible incremental cost–effectiveness ratio for fremanezumab compared with best supportive care for episodic mi-graine after failure of three preventive treatments was below £20 000 per QALY gained. Frem-anezumab was considered to be a

cost-effective use of National Health Service resources for people with episodic migraine in whom three preventative treatments had failed. With regard to chronic migraine, uncertainties remained about the clinical effectiveness of fremanezumab; however, fremanezumab was considered likely to be a cost-effective use of National Health Service resources for preventing chronic migraine after three preventive treatments had failed. Subsidized supply of fremanezumab in the United Kingdom is subject to a commercial arrangement with the manufacturer (*20*).

A 2024 company-sponsored analysis in the Kingdom of the Netherlands evaluated the cost–effectiveness of fremanezumab versus best supportive care in patients with chronic migraine and inadequate response to previous preventive therapy from a societal perspective including direct and indirect costs (*21*). The base-case analysis, which compared fremanezumab with best supportive care (acute migraine treatment only) in patients with chronic migraine and an inad-equate response to topiramate or valproate and onabotulinumtoxinA over a lifetime horizon, relied on data from a post hoc subgroup analysis of 138 patients from the FOCUS trial (*22*). The results from the base-case analysis found fremanezumab to be dominant strategy. A supportive analysis using data from the full FOCUS population with chronic migraine (509 patients) (*10*) found fremanezumab was cost-effective compared with best supportive care with an incremen-tal cost–effectiveness ratio of €2547/QALY gained. Fremanezumab remained cost-effective in all sensitivity and scenario analyses.

A 2024 company-sponsored analysis evaluated the cost–effectiveness of fremanezumab com-pared with standard care in previously treated patients with episodic and chronic migraine over a 25-year horizon from a Japanese health-care perspective (*23*). Incremental cost–effectiveness ratios for fremanezumab versus standard care were 6 334 861 Japanese yen (¥) (~US$ 41 345) for episodic migraine, ¥7 393 824 (~US$ 48 257) for chronic migraine and ¥6 530 398 (~US$ 42 621) for the total migraine population (weighted average of 70% episodic and 30% chronic). Higher incremental cost–effectiveness ratios of ¥9 442 917 to ¥9 952 007 (~US$ 61 630 to US$ 64 953) were found in scenarios that excluded productivity losses. Assum-ing a willingness-to-pay threshold of ¥5 million (~US$ 32 633), fremanezumab would have about a 26% chance of being cost effective compared with standard care.

Availability

A survey conducted among members of the International Headache Society reported that fremanezumab was available in 29 upper-middle and high-income countries globally. Biosimilar versions are not currently available.

Other considerations

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Committee recommendations

The Expert Committee noted that migraine is a common primary headache disorder characterized by recurrent moderate to severe pain and acknowledged the public health relevance of effective treatments. Migraine is a cause of considerable disability and results in a substantial socioeconomic burden, which is greater for women than for men. Migraine prophylaxis is generally recommended in the presence of at least four migraine days per month and/or when migraine substantially affects quality of life. The Committee acknowledged the importance of preventive treatment in people with chronic migraine, occurring in about 2% of the population and defined as at least 15 days with headache per month for at least 3 months. With daily or near-daily attacks, people with chronic migraine have functional impairment and a lower quality of life.

The Committee noted that multiple randomized, double-blind, placebo-controlled trials demonstrated the benefits of fremanezumab over placebo in reducing the monthly average migraine days and increasing the ≥ 50% responder rate in patients with episodic and chronic migraine. Subgroup analyses (e.g. based on previous treatment failures) also suggested that fremanezumab was effective in refractory populations and may improve disability and quality of life. The Committee considered that the magnitude of benefit of fremanezumab over placebo was moderate and greater in patients with episodic migraine than chronic migraine. Adverse events of fremanezumab were generally mild to moderate in severity and were manageable.

The Committee also noted the findings of a recent systematic review and network meta-analysis of the different classes of medicine for migraine prophylaxis which reported high-, moderate-, and low-certainty evidence (depending on the comparator) that fremanezumab may have a greater effect and a better safety profile than medicines from other classes. However, the review did not include trials involving fremanezumab in direct head-to-head comparisons with other medicines (e.g. propranolol); therefore, the Committee was unable to determine the magnitude of benefit of fremanezumab versus the currently listed prophylactic treatment.

The Committee noted that fremanezumab was considerably more expensive than propranolol and concluded that, in the absence of clear evidence demonstrating a proportional improvement in outcomes, the cost difference could not be justified to support a recommendation to list on the EML at this time.

The Committee also noted the current limited global availability of the medicine and that biosimilar versions are not yet available.

Based on these considerations, the Expert Committee did not recommend the inclusion of fremanezumab on the EML for prophylaxis of high-frequency or chronic migraine.

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Prednisolone, sumatriptan, and verapamil – new indication – EML

Prednisolone	**ATC code: H02AB07**
Sumatriptan	**ATC code: N02CC01**
Verapamil	**ATC code: C08DA01**

Proposal

Extension of the indications for the listing of sumatriptan on the EML to include acute treatment of cluster headache in adults, and extension of the indications for the listings of prednisolone and verapamil on the EML to include prevention of cluster headache in adults.

Applicant

European Headache Federation; International Headache Society; Lifting the Burden; and Disease Relief by Excellent and Advanced Means

WHO technical department

The Department of Mental Health, Brain Health and Substance Use provided comments on the application and supported the proposal. They also highlighted a need for a review of the evidence for oxygen therapy for cluster headache, which has been shown to be an effective first-line treatment for acute attacks.

EML/EMLc

EML

Section

5.1.5.3 Medicines for cluster headache

Dose form(s) & strengths(s)

Sumatriptan

Injection, subcutaneous: 6 mg/0.5 mL in prefilled syringe or pen

Prednisolone

Tablet: 5 mg, 25 mg

Verapamil

Tablet, immediate-release: 40 mg, 80 mg, 120 mg

Tablet, extended-release: 120 mg, 180 mg, 240 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Medicines for the treatment and prevention of cluster headache have not previously been evaluated for inclusion on the EML. Sumatriptan, prednisolone and verapamil are all already included on the EML for other indications.

Currently listed medicines for the treatment and prophylaxis of migraine are not effective in the management of cluster headache.

Public health relevance

Cluster headache is a severe, debilitating primary headache disorder affecting about 1 in 1000 people globally, with a higher prevalence in men than in women (*1*). It is characterized by periods, lasting weeks or months, of frequently recurring short attacks of excruciating unilateral pain, typically around the eye or temple, usually accompanied by extreme agitation and autonomic symptoms such as tearing, nasal congestion and ptosis (*2*). Attacks may recur several times a day and substantially affect the productivity and quality of life of those affected both during attacks and throughout the cluster period. Cluster headache is associated with substantial health and economic burdens, with high health-care costs (*3*).

Summary of evidence: benefits

Sumatriptan

A 2013 Cochrane systematic review and meta-analysis of six randomized controlled trials evaluated the efficacy and tolerability of triptans compared to placebo and other active interventions for acute treatment of cluster headache in adults (*4*). The review found low-quality evidence that subcutaneous sumatriptan 6 mg was significantly superior to placebo for the primary outcomes of pain-free at 15 minutes (risk ratio (RR 2.72, 95% confidence interval (CI) 1.82 to 4.21; two randomized controlled trials, 258 participants, number needed to treat (NNT) = 4) and headache relief at 15 minutes (RR 2.31, 95% CI 1.77 to 3.03; two randomized controlled trials, 258 participants, NNT = 3). The proportions of attacks that were pain-free at 15 minutes were 48% and 15% for sumatriptan and placebo, respectively. The proportions of attacks with headache relief at 15 minutes were 78% and 32% for sumatriptan and placebo, respectively.

A 2022 network meta-analysis of 13 randomized controlled trials evaluated the relative effectiveness and harms of acute treatment options for cluster headache (*5*). Interventions included high- and low-flow oxygen, subcutaneous sumatriptan, nasal zolmitriptan, octreotide, and non-invasive vagal nerve stimulation. For the outcome of headache response at 15 and 30

minutes compared to placebo, high-flow oxygen was the most effective (odds ratio (OR) 9.0, 95% credible interval (CrI) 5.3 to 15.9), followed by subcutaneous sumatriptan (OR 6.4, 95% CrI 3.8 to 11.1). Subcutaneous sumatriptan was more effective than all other interventions studied, with the exception of oxygen.

Prednisone/prednisolone

Note: The study described below investigates prednisone, the prodrug of prednisolone. They are generally considered to be equally effective and safe.

A 2021 randomized, multicentre, double-blind, placebo-controlled trial in Germany evaluated the efficacy and safety of prednisone in the short-term prevention of episodic cluster headache (*6*). Participants were randomized 1:1 to receive 100 mg prednisone for 5 days followed by a tapering of 20 mg every 3 days, or matching placebo while being titrated up to prophylactic verapamil 120 mg three times daily. Study duration was 28 days and the primary endpoint was the mean number of attacks within the first week of treatment. Results showed that participants in the prednisone group had a significantly lower mean number of attacks within the first week compared with those in the placebo group (7.1 standard deviation (SD) 6.5 versus 9.5 SD 6.0), a difference of −2.4 attacks (95% CI −4.8 to −0.03).

Prednisone or prednisolone are primarily used in the short term as bridging treatment to other prophylactic treatments for cluster headache.

Verapamil

The applicants identified and described 10 heterogeneous studies (including two randomized controlled trials) that evaluated the effectiveness of verapamil as prophylactic treatment for cluster headache (*7*–*16*). The studies differed in design, interventions and outcome measures, but all reported benefit for verapamil. Pooled analysis of four non-comparative observational studies that reported outcomes of complete response or ≥ 50% reduction in attack frequency showed that 73% of patients who received verapamil reached either a complete response or ≥ 50% reduction in the attack frequency. Of the two randomized controlled trials, one was a small ($n = 30$) double-blind crossover trial comparing verapamil 360 mg daily versus lithium 900 mg daily in patients with chronic cluster headache. Both medicines were associated with significant improvements in headache index (improvement after the first 7 days of treatment) and analgesic consumption (*11*).The other was a small ($n = 30$) placebo-controlled trial in patients with episodic cluster headache that showed that verapamil 360 mg decreased daily attack frequency (mean 0.66, SD 0.88 versus. 1.65, SD 1.01) and daily analgesic use (mean 0.5, SD 0.87 versus. 1.2, SD 1.03) (*12*).

Summary of evidence: harms

The safety profiles of sumatriptan, prednisolone and verapamil are well known from their use in other indications.

Sumatriptan is associated with a potential risk of cardiovascular events and is contraindicated in people with a history of ischemic heart disease, uncontrolled hypertension or cerebrovascular disease. Subcutaneous administration of sumatriptan is associated with mild, transient injection site reactions, tingling and pressure sensations (*17*).

Short-term use of prednisolone is generally considered safe. Commonly reported adverse events include increased appetite, mood swings and insomnia. Long-term use is associated with greater risks, including adrenal suppression, osteoporosis and increased susceptibility to infection (*3*).

Common adverse events associated with verapamil include constipation, dizziness, fatigue and oedema, which are usually mild and manageable with dose adjustment (*18*). Verapamil can lead to heart block, therefore baseline and periodic electrocardiograph monitoring to detect potential cardiac issues is recommended.

Additional evidence

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WHO guidelines

WHO guidelines for the management of cluster headache are not currently available.

The application provided a brief summary of recommendations on subcutaneous sumatriptan, prednisone/prednisolone and verapamil as key treatments for cluster headache from various current national and international clinical guidelines.

Costs/cost–effectiveness

The application stated that economic studies of the proposed medicines for the treatment or prevention of cluster headache are not available. De novo modelled cost–effectiveness assessments were presented instead.

For acute treatment with sumatriptan, costs per healthy life year gained were calculated to be 120 623 United States dollars (US$) and US$ 47 892, depending on the price input. For prophylactic treatment with prednisolone and verapamil, cost per healthy live year gained was calculated as US$ 37 875. When a stopping rule was applied whereby repeated use in subsequent cluster periods was limited to only individuals with a good response in the first cluster period, the cost per healthy life year gained was US$ 1544.The analyses for prophylactic treatment did not account for interictal lost health, which is expected to be averted by the reduction in duration of cluster periods.

Availability

Subcutaneous sumatriptan has wide regulatory approval for use in the acute treatment of cluster headache. Availability of the subcutaneous formulation may be limited in some settings. Generics are available.

The use of prednisolone and verapamil for prophylaxis of cluster headache is off-label. Both medicines are widely available in generic forms.

Other considerations

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Committee recommendations

The Expert Committee noted that cluster headaches are a severe and debilitating type of headache, for which the need for prompt treatment of acute attacks and prophylaxis is important to reduce the effect of the condition on sufferers. The Committee also noted that there are currently no treatments for cluster headache on the EML and that the medicines currently listed for acute treatment and prophylaxis of migraine are ineffective for cluster headache.

The Committee noted that high-flow oxygen treatment and triptans are the recommended treatment for acute attacks, while verapamil is the most widely prescribed medication for prophylaxis. Glucocorticoids are also recommended as preventive therapy for people with episodic cluster headaches and infrequent active cluster periods but are primarily used as bridging therapy to prophylactic treatment.

The Committee considered that the evidence presented in the application supported the efficacy and safety of subcutaneous sumatriptan for the acute management of cluster headache attacks, offering rapid symptom relief. However, the Committee also noted the role of inhaled oxygen in this setting, which may be associated with higher efficacy than subcutaneous sumatriptan.

The Committee noted that the evidence supporting the use of verapamil as a first-line preventive treatment of cluster headache was limited. However, pooled estimates indicated that most people treated achieved either a complete response or a more than 50% reduction in attack frequency compared with placebo. With regard to safety, the Committee noted the need for dose titration when starting or stopping verapamil and that regular electrocardiographs are recommended to monitor cardiac function. Overall, the Committee considered that verapamil had a favourable balance of benefits and harms in this condition.

In consideration of prednisolone, the Expert Committee noted that corticosteroids may be used for short-term bridging therapy during the start or adjustment of prophylactic treatments. The evidence reported in the application was for prednisone, an inactive prodrug that is metabolized to prednisolone

in the liver. Prednisone and prednisolone are used to treat similar conditions and are generally considered equally effective and safe. In people with reduced hepatic function, prednisolone is usually preferred. The Committee considered that the available evidence supported the efficacy of prednisone (and by inference, prednisolone) as a rapid-acting, short-term preventive treatment for episodic cluster headache that can be used to attenuate the early cluster episode until long-term prevention has reached its full efficacy. With regard to safety, the Committee recalled the well known adverse effect profile of prednisone/prednisolone and recognized that short term-use was associated with a better safety profile than longer-term use. Overall, the Committee considered that prednisone/prednisolone also had a favourable balance of benefits and harms in this condition

The Committee noted the cost–effectiveness assessments of the three medicines performed by the applicants but was unable to confidently judge the true cost–effectiveness due to substantial uncertainty in the inputs. However, the Committee considered that the medicines were generally low cost and affordable, with availability of generics.

Based on these considerations, the Expert Committee recommended the inclusion on the core list of the EML of:

i. subcutaneous sumatriptan for the acute treatment of cluster headache attacks;
ii. prednisolone, as the representative medicine with prednisone as a therapeutic alternative, as bridging therapy for prophylactic treatment of cluster headache; and
iii. verapamil for prophylactic treatment of cluster headache.

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Section 6: Anti-infective medicines

6.1 Anthelminthics

6.1.2 Antifilarials

Moxidectin – addition – EML and EMLc

Moxidectin **ATC code: P02CX03**

Proposal

Addition of moxidectin to the core list of the EML and EMLc for treatment of adults and children aged 4 years and older with onchocerciasis and lymphatic filariasis as a therapeutic alternative to ivermectin.

Applicant

Medicines Development for Global Health (MDGH) Limited, Melbourne, Australia

WHO technical department

The Department of Control of Neglected Tropical Diseases indicated its support for the inclusion of moxidectin on the Model Lists as a therapeutic alternative to ivermectin for the proposed indications.

EML/EMLc

EML and EMLc

Section

6.1.2 Antifilarials

Dose form(s) & strengths(s)

Tablet: 2 mg

Core/complementary

Core

Individual/square box listing

Square box listing for ivermectin with moxidectin as a specified therapeutic alternative. Both medicines are of the macrocyclic lactone class of anthelminthics.

Background

Moxidectin has not previously been evaluated for inclusion on the Model Lists.

The Model Lists currently include ivermectin for the treatment of onchocerciasis and lymphatic filariasis, and albendazole and diethylcarbamazine for the treatment of lymphatic filariasis.

Public health relevance

The public health relevance of effective and safe anthelminthic treatment is well established.

In 2022 at least 246 million people worldwide required preventive chemotherapy against onchocerciasis (*1*). The prevalence of onchocerciasis in 2021 was 19.6 million (95% uncertainty interval (UI) 17.8 to 21.7 million), an increase of 17.7% compared with 2010. In 2021, onchocerciasis was responsible for the loss of 1.26 million (95% UI 0.75 to 1.90 million) disability-adjusted life years (DALYs). Key sequelae contributing to DALYs are moderate to severe skin disease and blindness (*2*).

Estimates in 2022 indicate that about 794 million people worldwide required preventive chemotherapy against lymphatic filariasis (*3*). The prevalence of lymphatic filariasis in 2021 was 56.9 million (95% UI 48.7 to 67.9), a decrease of 39.9% compared with 2010. In 2021, lymphatic filariasis was responsible for the loss of 1.31 million DALYs (95% UI 0.77 to 2.22 million DALYs). Key sequelae contributing to DALYs are lymphoedema and hydrocele (*4*).

Both onchocerciasis and lymphatic filariasis are filarial diseases that have serious social and economic consequences, both to the individual and their communities, such as stigmatization due to their physical manifestations and the compounding of poverty which undermines development in endemic countries.

The WHO road map for neglected tropical diseases, 2021–2030, identified onchocerciasis as a disease targeted for elimination (interruption of transmission) and lymphatic filariasis for elimination as a public health problem (*5*). The targets to be reached by 2030 are:

- for onchocerciasis, to have at least 12 countries verified for elimination of transmission, and to have stopped mass drug administration in at least one focus in 34 countries, in more than 50% of the population in at least 16 countries and in the entire endemic population in at least 12 countries;
- for lymphatic filariasis, to eliminate the need for mass drug administration, implement post-mass drug administration or post-validation surveillance in all 72 endemic countries and achieve validation of elimination as a public health problem in 58 of 72 endemic countries.

Ivermectin, a first-generation macrocyclic lactone of the avermectin class, is presently used in mass drug administration programmes for the treatment of onchocerciasis and lymphatic filariasis in endemic regions, in accordance with the following WHO recommendations.

- In areas where onchocerciasis is endemic (in the absence of lymphatic filariasis or loiasis), the current WHO-recommended regimen for mass drug administration is ivermectin given annually (or biannually).
- In areas where lymphatic filariasis is endemic (in the absence of onchocerciasis or loiasis), the current WHO-recommended combination regimen for mass drug administration is annual diethylcarbamazine plus albendazole, or ivermectin, diethylcarbamazine and albendazole.
- In areas where lymphatic filariasis and onchocerciasis are co-endemic (in the absence of loiasis), the current WHO-recommended combination regimen for mass drug administration is annual ivermectin and albendazole.

Ivermectin is currently the only available treatment option for use in onchocerciasis and has been associated with unsustained and suboptimal responses. In studies on treatment for onchocerciasis, ivermectin failed to sustain skin microfilariae clearance for either 6 or 12 months (the two most commonly used ivermectin treatment intervals) in most infected individuals and microfilariae repopulation of the skin was shown to occur within 3 months of treatment (*6*, *7*). Given this situation, elimination in many places may not be achievable and targets may be difficult to reach. Therefore, one of the critical actions listed to achieve elimination targets is to implement alternative strategies for mass drug administration or improved interventions for onchocerciasis where appropriate.

Despite significant progress by the Global Programme to Eliminate Lymphatic Filariasis to eliminate lymphatic filariasis as a public health problem, infection rates in a variety of settings have remained above elimination targets, even after many rounds of treatment (*3*). Progress has been particularly poor in communities co-endemic for onchocerciasis, where the so-called gold standard diethylcarbamazine combinations cannot be used due to safety concerns. An alternative treatment with comparable efficacy to diethylcarbamazine combinations but without the safety risks is urgently needed to ensure these areas are not left behind.

In 2023, the WHO-hosted Global Accelerator for Paediatric formulations (GAP-f) network released the first list of priority paediatric formulations for five neglected tropical diseases to target research and development, and to address the specific needs of infants and children (*8*). Moxidectin for onchocerciasis and scabies was included as a priority in this list, reinforcing the public health need for this population.

Summary of evidence: benefits

Onchocerciasis

The application presented findings from a 2022 systematic review and meta-analysis of two randomized controlled trials that compared the efficacy and safety evidence of moxidectin and ivermectin for the control and elimination of onchocerciasis in adults and adolescents aged 12 years and older (9). Primary efficacy outcomes included: complete microfilariae clearance, defined as the proportion (%) of people with undetectable skin microfilariae at 6 or 12 months after treatment; duration of microfilariae clearance, assessed as the follow-up time at which the maximum proportion of individuals with undetectable skin microfilariae is achieved after treatment; and mean microfilariae densities and range before and at 6 or 12 months after treatment.

Pooled analysis showed increased odds of skin microfilariae clearance 12 months post-treatment in the moxidectin 8 mg group compared to the ivermectin 150 microgram/kg group (1495 participants, log odds ratio (OR) 2.81, 95% confidence interval (CI) 0.95 to 4.68; moderate-certainty evidence), corresponding to 48 more moxidectin treated patients per 1000 (95% CI 1 fewer to 93 more) achieving skin microfilariae clearance in absolute terms. Given that treatment with moxidectin will be given to populations co-infected with other neglected tropical diseases, a secondary objective of this systematic review was to assess the efficacy of moxidectin for the control and elimination of other filarial and helminth infections. The authors identified no added effect of moxidectin for the treatment and control of *Strongyloides stercoralis*, *Trichuris trichiura*, *Schistosoma haematobium* and *Schistosoma mansoni*. The available evidence showed that outcomes in these diseases would be similar to those with ivermectin. The evidence at the time of the review for lymphatic filariasis was insufficient to determine whether moxidectin could be used for annual mass drug administration to eliminate lymphatic filariasis in implementation units co-endemic for onchocerciasis (9).

The systematic search used for the above-mentioned systematic review was repeated by the applicants in August 2024. No new publications of relevance to the efficacy of moxidectin for the control and elimination of onchocerciasis were identified. However, three additional publications were identified as contributing to the evidence on the efficacy of moxidectin in other filarial and helminth infections.

A 2024 study reported efficacy findings of a double-blind, randomized, ivermectin-controlled trial comparing a 2 mg moxidectin dose and the standard 150 microgram/kg ivermectin dose for onchocerciasis in individuals with low loa loa microfilarial densities (10). The study was conducted in Cameroon and enrolled 72 adult men with loa loa microfilarial density between 5 and 1000

microfilariae/mL. A key outcome was the loa loa microfilarial density reduction rate in the first month after treatment. Median microfilarial density reduction rates were significantly higher after ivermectin than moxidectin at day 3 (70.2% versus 48.5%), day 7 (76.4% versus 50.0%) and day 30 (79.8% versus 48.1%). The authors concluded that further studies with higher doses of moxidectin (up to the standard dose of 8 mg used for treatment of onchocerciasis) and in patients with higher loa loa microfilarial densities are warranted.

A 2023 study reported efficacy findings from a community-based, randomized, placebo-controlled, parallel-group superiority trial of moxidectin 8 mg plus albendazole 400 mg and ivermectin 200 microgram/kg plus albendazole 400 mg combination therapy compared with albendazole monotherapy in adolescents and adults infected with *T. trichiura* in Côte D'Ivoire (*11*). The primary outcome was proportion cured (cure rate) assessed 2–3 weeks post-treatment. For the 210 participants with primary outcome data, cure rates were 15.3% in the moxidectin–albendazole arm and 22.5% in the ivermectin–albendazole arm, which did not differ significantly from the cure rate of 13.4% in the albendazole arm (differences: 1.8 percentage points (95% CI −10.1 to 13.6) and 9.1 percentage points (95% CI −3.9 to 21.8), respectively). The authors concluded that all therapies showed similar low efficacy in treating trichuriasis in Côte d'Ivoire.

Efficacy findings were reported from a randomized, double-blind, parallel-group, non-inferiority, phase IIb/III trial of a single oral dose of either moxidectin (8 mg) or ivermectin (200 microgram/kg bodyweight) for *Strongyloides stercoralis* infection in adults in Cambodia and Lao People's Democratic Republic (*12*). In total, 726 participants were enrolled and randomly assigned to moxidectin ($n = 363$) or ivermectin ($n = 363$). The primary endpoint was the cure rate assessed 14–21 days after treatment. For the participants with primary outcome data, cure rates were 93.6% (95% CI90.5 to 96.0; 324 of 346 participants) in the moxidectin group and 95.7% (95% CI 93.0 to 97.6; 335 of 350 participants) in the ivermectin group, a between-group difference of −2.1 percentage points (95% CI −5.5 to 1.3). The authors concluded that moxidectin was non-inferior to ivermectin in terms of efficacy in the treatment of strongyloidiasis.

The application presented unpublished data from Study MDGH-MOX-1006, a pharmacokinetic and safety study of moxidectin to identify the optimal treatment dose for children aged 4 to 11 years (*13*). Thirty-six participants in Ghana aged 4 to 17 years with or at risk of onchocerciasis were enrolled in three cohorts. A single dose of moxidectin was administered: 8 mg (cohort I; 12 to 17 years), 6 or 8 mg (cohort II; 8 to 11 years) or 4 mg (cohort III; 4 to 7 years). The data indicated that moxidectin doses of 6 mg in children aged 8 to 11 years and 4 mg in children aged 4 to 7 years provide comparable exposures to those achieved with a moxidectin dose of 8 mg in adolescents 12 years and older and adults. A simplified dosing regimen to support ease of operationalization

in field treatment programmes has been proposed and was investigated using the moxidectin population pharmacokinetic model and relevant weight-for-age growth charts. Simulations identified that an age-based regimen consisting of a 4 mg dose for children 4 to < 8 years and an 8 mg dose for children and adolescents ≥ 8 to 17 years provides a pharmacokinetically-optimized and simplified age-based alternative to three different doses across ages from 4 years to adults. Based on these data, regulatory approval applications have been submitted to the United States Food and Drug Administration and the Ghana Food and Drugs Authority. The safety of this dose regimen is currently being further examined in a clinical study in the Democratic Republic of the Congo and Côte d'Ivoire which is assessing the safety of single dose moxidectin compared with single dose ivermectin in participants 4 years and older (*14*).

Lymphatic filariasis

A phase III, randomized, open-label study evaluated the safety and efficacy of moxidectin combination treatments versus ivermectin combination treatments for lymphatic filariasis in adults in Côte d'Ivoire (*15*). Participants ($n = 164$) were randomly assigned to receive ivermectin 200 micrograms/kg plus albendazole 400 mg (IA), given annually; moxidectin 8 mg plus albendazole 400 mg (MoxA), given once; ivermectin 200 micrograms/kg plus diethylcarbamazine 6 mg/kg plus albendazole 400 mg (IDA), given once; or moxidectin 8 mg plus diethylcarbamazine 6 mg/kg plus albendazole 400 mg (MoxDA), given once. The primary outcome was the proportion of individuals in each group with clearance of *Wuchereria bancrofti* microfilariae at 12 months post-treatment. At 12 months post-treatment, the proportion of participants with microfilaria clearance was: 8/25 (32%) for IA versus 18/19 (95%) for MoxA (adjusted risk ratio (RR) 2.79, 95% CI 1.59 to 4.90); and 24/28 (86%) for IDA versus 27/28 (96%) for MoxDA (adjusted RR 1.07, 95% CI 0.90 to 1.27). Differences diminished 24 months after treatment: 13/25 (52%) for IA versus 14/16 (88%) for MoxA (adjusted RR 1.49, 95% CI 1.02 to 2.19), and 20/22 (91%) for IDA versus 21/23 (91%) for MoxDA (adjusted RR 0.98, 95% CI 0.83 to 1.15). The authors concluded that a single dose of MoxA was superior to IA for microfilaria clearance at 12 months and compared favourably with two annual doses of IA at 24 months. No difference was seen between MoxA and IDA or MoxDA for microfilaria clearance at 24 months.

Summary of evidence: harms

From the 2022 systematic review of moxidectin and ivermectin for the control and elimination of onchocerciasis, pooled analysis of two randomized controlled trials (1555 participants) showed moderate-certainty evidence of no significant difference between moxidectin and ivermectin in the occurrence of all adverse events after treatment (log OR 0.43, 95% CI −1.64 to 2.50) and serious adverse events

(log OR 0.15, 95% CI −0.42 to 0.73). In absolute terms, 37 fewer persons per 1000 experienced any adverse event after treatment with moxidectin compared with ivermectin (*9*). At the time of publication of the systematic review, the data available were insufficient to evaluate whether moxidectin was safe to use in implementation areas co-endemic for onchocerciasis and lymphatic filariasis or loiasis.

The systematic search used for the above-mentioned systematic review was repeated by the applicants in August 2024 and six additional studies relevant to the safety of moxidectin were identified.

A 2023 paper reported findings from a pharmacokinetic sub-study in 58 participants (ages 18 to 63 years) of the NCT04410406 trial on the pharmacokinetics and drug interactions of moxidectin 8 mg plus albendazole 400 mg with or without diethylcarbamazine 6 mg/kg compared to ivermectin 0.2 mg/kg plus albendazole 400 mg with or without diethylcarbamazine 6 mg/kg (*16*). The addition of moxidectin to albendazole with or without diethylcarbamazine for lymphatic filariasis therapy did not alter the drug exposure of co-administered drugs compared with ivermectin combinations.

The safety and tolerability of moxidectin and ivermectin combination treatments for lymphatic filariasis were assessed in the NCT04410406 trial in which 164 participants were treated and monitored for treatment-emergent adverse events (*17*). Eighty-seven participants (53.0%) experienced one or more grade 1 or grade 2 treatment-emergent adverse event. Grade 3 haematuria was reported in four participants (three after treatment with ivermectin plus diethylcarbamazine plus albendazole, and one after treatment with ivermectin plus albendazole). No serious adverse events were reported and no significant differences in frequency or types of treatment-emergent adverse events between treatment groups were reported. Grade 2 treatment-emergent adverse events were more frequent after triple drug treatments (ivermectin plus diethylcarbamazine plus albendazole, 14.6%; moxidectin plus albendazole, 9.5%) than after two-drug treatments (ivermectin plus albendazole, 7.3%; moxidectin plus albendazole, 2.5%). No difference in treatment-emergent adverse events based on baseline microfilariae counts was seen (OR 0.69, 95% CI 0.33 to 1.43; $P = 0.319$). The authors concluded that all treatment regimens were well tolerated and no difference in safety parameters between regimens that contained ivermectin or moxidectin were observed.

Another study reported safety findings from a double-blind, randomized, controlled trial comparing a single 2 mg moxidectin dose and 150 microgram/kg ivermectin dose in 72 participants with low loa loa microfilarial density (between 5 and 1000 microfilariae/mL) (*10*). The safety outcome was occurrence of adverse events in the first month of treatment. A total of 49 and 59 adverse events were reported in the moxidectin and ivermectin groups, respectively. No serious or severe adverse events occurred in either treatment group. The incidence of

grade 2 adverse events was higher among participants treated with ivermectin than moxidectin (38.5% and 14.3%, respectively; $P = 0.043$). The most frequently reported clinical adverse events with moxidectin were headache, fatigue, pruritus and fever. The most frequent laboratory abnormality was grade 1 creatinine increase, occurring in 25.7% and 18.2% of participants in the moxidectin and ivermectin groups, respectively. Neutropenia occurred in 8.6% and 18.2% of the participants in the moxidectin and ivermectin groups, respectively. The authors concluded that a single 2 mg moxidectin dose had a similar safety profile to 150 microgram/kg ivermectin in patients with low loa loa microfilariae density.

Data were analysed from a randomized, double-blind phase III trial comparing the efficacy and safety of a single oral dose of 8 mg moxidectin and 150 microgram/kg ivermectin in 1463 participants with *Onchocerca volvulus* infection (*18*). The outcomes were ocular adverse events observed within 6 months of treatment. Ocular Mazzotti reactions occurred in 12.4% and 10.2% of moxidectin- and ivermectin-treated participants, respectively, without differences in type or severity. The risk for at least one ocular Mazzotti reaction was higher in women (OR 1.54, 95% CI 1.10 to 2.16) and in participants with microfilariae levels in the anterior chamber > 10 at screening (OR 2.70, 95% CI 1.27 to 5.75) and 4 days post-treatment (OR 1.619, 95% CI 0.80 to 3.28).

Safety findings were reported from a community-based, randomized, placebo-controlled, parallel-group superiority trial of moxidectin 8 mg plus albendazole 400 mg and ivermectin 200 microgram/kg plus albendazole 400 mg combination therapy compared with albendazole monotherapy in adolescents and adults infected with *T. trichiura* in Côte D'Ivoire (*11*). Safety endpoints were assessed pre-treatment and at 3 and 24 hours post-treatment. In total, 102/255 (40.0%) participants experienced an adverse event: 37/86 (43.0%) who received ivermectin plus albendazole; 34/85 (40.0%) who received moxidectin plus albendazole; and 31/84 (36.9%) who received albendazole monotherapy. The most common adverse events were abdominal pain, headache and itching, and were predominantly mild and transient.

Safety findings were also reported from a randomized, double-blind, parallel-group, non-inferiority, phase IIb/III trial of single oral doses of moxidectin 8 mg ($n = 363$) or ivermectin 200 microgram/kg ($n = 363$) for *S. stercoralis* in 726 adults in Laos and Cambodia (*12*). Safety endpoints were assessed before treatment, and 2–3 hours, 24 hours, and 14–21 days after treatment. Following treatment, 153 (21.1%) participants experienced an adverse event: 74 (20.4%) who received moxidectin and 79 (21.8%) who received ivermectin. The most common adverse events were abdominal pain and headache and were predominantly mild and transient.

Additional evidence

The application also presented details of other ongoing trials of moxidectin, for which results are not yet available. These include a randomized phase IIIb trial comparing efficacy and safety of annual and biannual doses of moxidectin or ivermectin for treatment of onchocerciasis, and a randomized phase II dose-finding study of moxidectin for the treatment of scabies.

WHO guidelines

WHO guidelines for the treatment of onchocerciasis are not currently available. Treatment recommendations for onchocerciasis on the WHO website currently recommend treating onchocerciasis with ivermectin at least once yearly for 10 to 15 years (*19*). This is reiterated in the WHO guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis where the current intervention strategy for onchocerciasis is based on mass drug administration with ivermectin (*20*). This treatment regimen may need to be adjusted in regions where onchocerciasis is co-endemic with loiasis, another filarial disease caused by the loa loa parasite, as treating individuals with high levels of the loa loa parasite with ivermectin may cause serious adverse events (*3*). The 2017 WHO guideline for alternative mass drug administration regimens to eliminate lymphatic filariasis recommends various preventive chemotherapy strategies, depending on the co-endemicity of lymphatic filariasis with other filarial diseases (*21*). The recommendations include:

- biannual albendazole 400 mg for areas co-endemic with loiasis;
- annual ivermectin 200 microgram/kg plus albendazole 400 mg in countries co-endemic with onchocerciasis;
- annual diethylcarbamazine 6 mg/kg plus albendazole 400 mg in countries without onchocerciasis; and
- annual ivermectin 200 microgram/kg plus diethylcarbamazine 6 mg/kg plus albendazole 400 mg in communities without onchocerciasis and where other programmatic conditions are met.

Costs/cost–effectiveness

The application reported that at the current production capacity of 1.9 million treatments per year, a proposed price of moxidectin per 8 mg dose is 1.56 United States dollars (US$). The applicant anticipates that with production scaled to about 30.6 million 8 mg treatments, the ex-manufacturer cost per treatment will decrease by more than half (excluding the cost of tooling and manufacturing upgrade that would be required). Shipping and transportation costs are not included in these estimates.

In 1987, Merck committed to donating ivermectin to help eliminate onchocerciasis. This commitment expanded in 1998 to include the treatment of lymphatic filariasis. Over 35 years, the Mectizan® Donation Program has grown from 0.3 million treatments to 376.4 million treatments in 2023, corresponding to about 1.355 billion tablets of ivermectin a year. While the actual cost of this ivermectin treatment is not publicly known, the declared market value of the donated treatment is US$ 4.50 per treatment, and Merck benefits from a tax exemption from the United States government for this donation (*22*).

The impact of moxidectin has been studied in mathematical models. A 2015 modelling study based on data from a phase II onchocerciasis clinical trial and using the population based deterministic EPIONCHO epidemiological model reported that both annual moxidectin and biannual ivermectin mass drug administration would achieve similar reductions in programme duration relative to annual ivermectin treatment (*23*). A 2024 study investigated annual and biannual community-directed treatment with ivermectin (aCDTI and bCDTI) and moxidectin (aCDTM and bCDTM) in various scenarios of the percentage of the total population receiving treatment and microfilarial baseline prevalence, comparing programmatic delivery costs (excluding drug costs) for the number of treatments achieving a 90% probability of elimination of parasite transmission (*24*). The assumed economic cost of aCDTI or aCDTM) was US$ 50 535 per 100 000 individuals. The results suggested that aCDTM and bCDTM could achieve a 90% probability of elimination of parasite transmission in a shorter programme duration and at lower programmatic delivery costs than aCDTI under all scenarios within 40 years. The sole exception was aCDTM with minimal population coverage in settings with hyperendemic baseline prevalence. For example, assuming minimal coverage in areas with 50% baseline disease prevalence, aCDTM would, with 90% probability, reduce the time to achieving elimination of transmission by 20 years compared with aCDTI, which in turn would translate into a reduction of programmatic costs by 36%. Projections were sensitive to assumptions about the relative permanent adult worm sterilizing effects of moxidectin compared with ivermectin, and the change in total delivery costs when treatment frequency changes.

Availability

Moxidectin has been approved by the United States Food and Drug Administration and the Ghana Food and Drugs Authority for the treatment of onchocerciasis due to *O. volvulus* in patients aged 4 years and older.

Moxidectin is currently produced with lead time and as required in bottles of 500 tablets. As the scenarios in which moxidectin will be used become more defined, and in collaboration with its funding partners, Medicines Development for Global Health will scale up production capacity to meet the growing demand

from endemic countries. This may require prioritization of these scenarios and/or working with specific priority countries to balance demand and supply-capacity ramp up in the near term.

Moxidectin is not currently included on any national essential medicines lists.

Moxidectin 2 mg tablets were included in the ninth invitation for expressions of interest for finished pharmaceutical products for neglected tropical diseases for WHO prequalification in October 2024. It is the intention of the applicant to engage with the WHO prequalification unit to support registration of moxidectin for the treatment of onchocerciasis and lymphatic filariasis.

Other considerations

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Committee recommendations

The Expert Committee recognized the public health importance of effective treatments for the control and elimination onchocerciasis and lymphatic filariasis. These neglected tropical diseases affect millions of people, primarily in sub-Saharan Africa, and result in serious social and economic consequences. The Committee noted with concern the predictions that WHO elimination targets for onchocerciasis and lymphatic filariasis may not be reached by 2030 with existing elimination strategies.

Based on the evidence presented, the Committee considered that moxidectin demonstrated superior efficacy and comparable safety compared with ivermectin for onchocerciasis and has regulatory approval for adults and children from 4 years for this indication. The Committee noted the evidence for moxidectin in lymphatic filariasis (published after the submission deadline but prior to the Expert Committee meeting) which demonstrated superior efficacy of a single dose of moxidectin plus albendazole over the current standard of care of annual doses of ivermectin plus albendazole, and comparable efficacy to other treatment regimens (e.g. ivermectin plus albendazole plus diethylcarbamazine). Moxidectin was equally well tolerated as other treatment regimens. Overall, the Committee considered that the balance of benefits to harms for moxidectin was favourable.

The Committee expressed some concern about the current limited availability of moxidectin, and financial implications of its use, considering that moxidectin would need to be procured whereas ivermectin is currently donated for mass drug elimination programmes. The Committee was encouraged by the support of the technical department for listing of moxidectin and their advice that moxidectin is being considered for inclusion in the WHO guidelines currently under development. The Committee also noted that moxidectin 2 mg tablets were included on an invitation to manufactures of medicinal products for neglected tropical diseases to submit an expression of interest for WHO

prequalification, and the advice of the manufacturer of their intention to consider pursuing prequalification. The Committee considered that moxidectin may offer an advantage over ivermectin for reducing overall programmatic costs by virtue of a potential to reduce the number of administration cycles needed to achieve disease elimination.

Based on these considerations, the Committee recommended the inclusion of moxidectin on the core list of the EML and EMLc as a therapeutic alternative to ivermectin for use in mass drug administration programmes for the control and elimination of onchocerciasis and lymphatic filariasis in adults and children.

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6.1.3 Antischistosomals and other antitrematode medicines

Arpraziquantel – addition – EMLc

Arpraziquantel **ATC code: P02BA03**

Proposal

Addition of arpraziquantel to the core list of the EMLc for the treatment of schistosomiasis caused by *Schistosoma mansoni* or *S. haematobium* in preschool-aged children from 3 months to 6 years.

Applicant

Merck Healthcare KGaA, Darmstadt, Germany

WHO technical department

The Department of Control of Neglected Tropical Diseases reviewed the application and provided comments. The department was hesitant about inclusion of arpraziquantel on the EMLc at this time, citing its current lack of market authorization and availability, its suboptimal strength resulting in a high pill burden and financial implications, especially given the need for procurement in contrast to praziquantel which is donated.

EML/EMLc

EMLc

Section

6.1.3 Antischistosomals and other antitrematode medicines

Dose form(s) & strengths(s)

Tablet (dispersible): 150 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Arpraziquantel has not been previously evaluated for inclusion on the Model Lists.

Praziquantel (40 mg/kg, single dose) is recommended by WHO for the treatment of schistosomiasis in adults and school-aged children (*1*) and

is currently included in the EML and EMLc as 150 mg, 500 mg and 600 mg conventional tablets for this indication. Arpraziquantel contains the biologically active enantiomer (R-(-)-praziquantel) of praziquantel and shares the same mechanism of action.

Public health relevance

Schistosomiasis, caused by parasitic flatworms (blood flukes), is one of the most neglected tropical diseases and is endemic in 78 countries, with moderate to high transmission kinetics in 51 of these countries. WHO estimates that 779 million people are at risk of acquiring a Schistosoma infection with more than 236 million people in 51 countries requiring preventive chemotherapy for schistosomiasis. Over 50% of infections in endemic countries are in children younger than 14 years (*1*).

Schistosomiasis in preschool-aged children has been linked to anaemia (*2*,*3*), decreased immune responses to vaccines (*4*), co-morbidities due to schistosomiasis egg trapping and subsequent inflammatory local responses (*4*–*6*), reduced quality of life, cognitive impairment and educational loss (*7*–*13*).

The WHO road map for neglected tropical diseases 2021–2030 targets the elimination of schistosomiasis as a public health problem globally by 2030 (*14*).

Praziquantel is well established as the standard treatment for schistosomiasis. However, praziquantel tablets need to be divided, crushed and given with water for dosing in young children. Furthermore, the bitter taste of the solution triggers gagging or vomiting and has negative implications for treatment compliance (*15*). Additionally, using the relationship between height and weight to predict bodyweight in children increases the risk of under- or over-dosing from dose adjustments when crushing and dividing praziquantel tablets, with a variance of up to 30% of the optimal dose (*16*).

Summary of evidence: benefits

The application reported that the efficacy of arpraziquantel has been demonstrated in phase II and III clinical studies. In the clinical development programme for arpraziquantel, 442 children aged 3 months to 6 years were treated with arpraziquantel. The cure rates achieved with arpraziquantel 50 mg/kg in S. mansoni infection and 60 mg/kg in S. haematobium infection were high (> 85% and 95%, respectively). The egg reduction rates were > 90% in both species.

An open-label, partly randomized phase III study evaluated the efficacy, safety, palatability and pharmacokinetics of arpraziquantel dispersible tablets in 288 children aged 3 months to 6 years infected with *S. mansoni* or *S. haematobium* in Côte d'Ivoire and Kenya (*17*). Participants were divided into four cohorts. In cohort 1, participants aged 4–6 years with *S. mansoni* infection were randomly assigned (2:1) to receive a single dose of oral arpraziquantel 50 mg/kg (cohort 1a)

or oral praziquantel 40 mg/kg (cohort 1b). Participants with *S. mansoni* infection in cohorts 2 (aged 2–3 years) and 3 (aged 3 months to 2 years), received a single dose of oral praziquantel 50 mg/kg. The first 30 participants in cohort 4a (aged 3 months to 6 years) infected with *S. haematobium* received a single dose of oral arpraziquantel 50 mg/kg. After follow-up assessments, the dose was increased to 60 mg/kg (cohort 4b).

For participants with *S. mansoni* infection in cohorts 1a, 2 and 3, cure rates with arpraziquantel 50 mg/kg were 87.8% (95% confidence interval (CI) 79.6% to 93.5%), 93.1% (95% CI 77.2% to 99.2%) and 94.4% (95% CI 72.7% to 99.9%), respectively. The cure rate in cohort 1b for participants receiving praziquantel was similar (81.3%, 95% CI 67.4% to 91.1%). For participants with *S. haematobium* infection in cohorts 4a and 4b, the cure rates at week 3 were 58.6% (95% CI 35.9% to 76.5%) and 86.2% (95% CI 74.6% to 93.9%). Subgroup analyses indicated that cure rates were independent of sex and were similar between countries. Higher cure rates were seen in participants with light infection intensity than in those with moderate or heavy infection intensity (*17*). Group geometric mean egg reduction rates ranged from 98.8% (95% CI 97.5% –99.7%) to 99.7% (99.5% to 99.9%) in all cohorts.

Palatability was assessed in participants aged 5–6 years from cohorts 1 and 4, using a modified 100 mm visual analogue scale. The median palatability score of arpraziquantel was greater than praziquantel (84 mm (interquartile range (IQR) 54 mm to 91 mm) versus 50 mm (IQR 26 mm to 87 mm) (*17*).

Summary of evidence: harms

Arpraziquantel is the biologically active enantiomer of racemic praziquantel. Thus, the safety profile of arpraziquantel is expected to be consistent with that of the well characterized formulations of racemic praziquantel (*18*–*20*).

In the above-mentioned phase III partly randomized trial, treatment-emergent adverse events occurred in 168/288 (58%) participants, including serious treatment-emergent adverse events in four participants. The most frequently reported such events considered to be treatment-related were abdominal pain (14%), diarrhoea (9%), somnolence (7%) and vomiting (6%). The incidence rates of any treatment-emergent adverse event and treatment-related adverse events were comparable between children aged 4–6 years receiving arpraziquantel 50 mg/kg and praziquantel 40 mg/kg: 66/100 (66%) versus 31/50 (62%) and 31/100 (31%) versus 14/50 (28%), respectively (*17*).

The application reported the following safety data from the clinical development programme of arpraziquantel to show that the safety profile of single doses of arpraziquantel in children aged 3 months to 6 years was consistent with the known safety profile of racemic praziquantel.

- Analysis of a pooled safety analysis dataset that included data from paediatric participants in phase II and III studies showed the

frequency of treatment-emergent adverse events was reported as 59.4%, 62.5% and 62.2% of participants treated with praziquantel tablets, praziquantel dispersible tablets and arpraziquantel, respectively. The incidence of arpraziquantel-related treatment-emergent adverse events or serious treatment-emergent adverse events was low (< 20% overall) and was generally similar across treatment groups. No treatment-emergent adverse events leading to death or discontinuation on the study were reported.

- The most frequently reported treatment-emergent adverse event was anaemia, which was reported in 24.7% of participants in the praziquantel tablet group, 37.5% in the praziquantel dispersible tablet group and 19.0% in the arpraziquantel group. Other reported treatment-emergent adverse events, including abdominal pain, diarrhoea, malaria and vomiting were observed with incidences that were consistent with the population under study and with concomitant conditions. These events were reported at similar rates across study interventions, with the exception of abdominal pain and vomiting, which were observed at a lower frequency in participants receiving praziquantel dispersible tablets than those receiving praziquantel tablets or arpraziquantel.
- No evidence was found of a dose-response relationship related to incidence and severity of treatment-emergent adverse events within the dose range studied.
- The treatment-emergent adverse event reporting rate was similar to the rates for the praziquantel tablet group and seemed to be associated with *Schistosoma* species and infection intensity.

In the arpraziquantel clinical development programme, only 43 children were younger than 2 years. Of these children, 41 received a dose of 50 mg/kg and two received 60 mg/kg. The safety profile of arpraziquantel in children 2 years and younger seems to be similar to the safety profile of arpraziquantel when used in older age groups, however, it remains uncertain due to the limited available data. Therefore, these results need to be interpreted with caution. The uncertainty is particularly relevant for children younger than 1 year.

The application highlighted the following potential safety concerns.

- The use of arpraziquantel in patients with undiagnosed asymptomatic neurocysticercosis may lead to seizures in these patients.
- Arrhythmia is listed as an adverse reaction with unknown frequency in the product information for racemic praziquantel. While no cases of arrhythmia have been reported for arpraziquantel, cardiac monitoring is suggested.

Additional evidence

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WHO guidelines

The 2022 WHO guideline on control and elimination of human schistosomiasis does not include recommendations for the use of arpraziquantel (*1*). In endemic communities with a prevalence of *Schistosoma* spp. infection ≥ 10%, the guideline recommends annual preventive chemotherapy with a single dose of praziquantel at ≥ 75% treatment coverage in all age groups from 2 years of age, including adults, pregnant women after the first trimester and lactating women, to control schistosomiasis morbidity and advance towards eliminating the disease as a public health problem (strong recommendation, moderate-certainty evidence).

Costs/cost–effectiveness

Arpraziquantel was developed specifically for the proposed paediatric population, after a target product profile that was defined in a consultation of experts and WHO (*21*). To date, no published cost–effectiveness studies or comparative cost information are available for this medicine in different markets.

The application stated that arpraziquantel is intended for public health programmes led by the ministries of health from endemic African countries and is expected to be available in the public sector for programme-based approaches or at public health-care facilities. Therefore, the medicine is expected to be free of charge for patients, or at government-subsidized affordable cost, if applicable within the health-care system of a country.

Availability

The application stated that arpraziquantel is not yet available. In December 2023, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive scientific opinion, in accordance with Article 58 of Regulation (EC) No. 726/2004, for arpraziquantel 150 mg dispersible tablets within the scope of the EU-medicines for all procedure for high-priority medicines for human use intended for markets outside the European Union. Marketing authorizations have not yet been submitted or granted for arpraziquantel but are foreseen in 2025 for some countries.

In May 2024, arpraziquantel 150 mg dispersible tablets were included in the WHO List of Prequalified Medicines.

With weight-based dosing, and based on the current estimation by WHO's Expanded Special Project for Elimination of Neglected Tropical Diseases that about 24 million preschool children aged 2–5 years old in about 48 African countries would require treatment via mass drug administration, the application

estimated that a maximum of 120 million tablets per year would be needed to cover 100% of this population. The manufacturing capacity that is currently set up would allow the needs of about 12 million preschool age children to be covered per year, based on the existing manufacturing capacity for the active pharmaceutical ingredient in China and once a Kenyan manufacturer is approved.

Other considerations

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Committee recommendations

The Expert Committee recognized the public health importance of effective treatments, in age-appropriate dosage forms, for the control and elimination schistosomiasis in children. The Committee noted that more than 50 million preschool-aged children are currently at risk of schistosomiasis in sub-Saharan Africa.

The Committee noted that arpraziquantel is the biologically active enantiomer of racemic praziquantel, the medicine currently included on the Model Lists (and recommended in WHO guidelines) for the treatment of schistosomiasis. For administration to preschool-aged children, praziquantel tablets need to be divided, crushed and given with water. The resultant solution has an unpalatable, bitter taste which may cause children to gag or vomit, thereby negatively affecting accurate dosing and treatment compliance.

In terms of benefits and harms, based on the evidence presented, the Committee noted that arpraziquantel was associated with high cure rates across age groups, with a similar cure rate to praziquantel. Adverse effects were consistent with the known adverse effects of praziquantel.

The Committee considered that the proposed formulation was age-appropriate for the target population, allowing precise dosing of children and infants of different body weights and with better palatability and acceptability than praziquantel for the target age group. However, the Committee also noted the high pill burden to achieve the required weight-based doses.

The Committee expressed concern that the application reported that the product was not yet available and that marketing authorization applications were planned in early adopter countries in 2025. However, the Committee also noted that the European Medicines Agency gave a positive scientific opinion of the product in 2023 in accordance with Article 58 for markets outside of the European Union and it was prequalified by WHO in 2024. The Committee also expressed concern about the financial implications of arpraziquantel use, given it would need to be procured, whereas praziquantel is currently donated.

The Committee considered the input from the WHO Department of Neglected Tropical Diseases, which considered the inclusion of arpraziquantel

150 mg dispersible tablets in the EMLc at this time to be premature, given that it is not currently available, and expressed a preference to wait for 300 mg dispersible tablets to become available.

Overall, the Committee considered that making an effective, safe, age-appropriate and palatable dosage form of arpraziquantel available should be prioritized, and that its inclusion on the EMLc could serve as an important signal to highlight this priority.

Therefore, the Expert Committee recommended the inclusion of arpraziquantel 150 mg dispersible tablets on the EMLc for treatment of schistosomiasis in preschool-aged children based on evidence of similar efficacy and safety with praziquantel, and better palatability and acceptability. Listing is recommended for arpraziquantel as a therapeutic alternative to praziquantel under a square box listing.

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6.2 Antibacterials

6.2.3 Reserve group antibiotics

Imipenem + cilastatin + relebactam – addition – EML

Imipenem + cilastatin + relebactam **ATC code: J01DH56**

Proposal

Addition of imipenem + cilastatin + relebactam to the complementary list of the EML as a reserve group antibiotic for treatment of confirmed or suspected infections due to multidrug-resistant organisms in adults.

Applicant

Merck, Sharp & Dohme, Rahway NJ, United States of America

WHO technical department

The WHO Control and Response Strategies Unit within the Division of Antimicrobial Resistance reviewed the application and advised that it did not support the inclusion of imipenem + cilastatin + relebactam on the EML. The technical unit highlighted that the circumstances that underpinned the 2023 Expert Committee's decision not to recommend inclusion had not changed.

EML/EMLc

EML

Section

6.2.3. Reserve group antibiotics

Dose form(s) & strengths(s)

Powder for injection: 500 mg (as monohydrate) + 500 mg (as sodium) + 250 mg (as monohydrate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application for the inclusion of imipenem + cilastatin + relebactam on the EML was evaluated by the Expert Committee in 2023. The Committee recognized

the global health importance of effective new treatments for infections caused by multidrug-resistant pathogens, especially those designated as critical priority on the WHO priority pathogens list, for which few effective treatment options exist or are in development. The Committee noted that imipenem + cilastatin + relebactam has broad in vitro activity against multidrug-resistant gram-negative pathogen but lacked in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally. The Committee also noted that other Reserve antibiotic options which have a similar spectrum of activity were already included on the EML for treatment of other types of carbapenem resistance in Enterobacterales (e.g. cefiderocol, ceftazidime + avibactam and meropenem + vaborbactam). The Committee considered that the available clinical trial evidence for efficacy was generally positive, although limited, and noted that no serious safety or tolerability concerns were identified. The Committee also noted the high price of the medicine compared with older antibiotics, but also that it had been found to be acceptably cost-effective at willingness-to-pay thresholds in high-income settings. Based on these considerations, the Expert Committee did not recommend listing at that time (*1*).

Public health relevance

Antimicrobial resistance is identified by WHO as one of the foremost global public health and developmental threats. Efforts to combat antimicrobial resistance, such as guaranteeing universal access to appropriate treatment options, are widely acknowledged as a critical public health priority (*2*).

A 2019 analysis estimated that 4.95 million people died with drug-resistant bacterial infections in 2019. Of these deaths, 1.27 million were directly attributable to resistant infections, most of which occurred in low- and middle-income countries. Drug resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli* were responsible for 84 600, 193 000 and 219 000 deaths, respectively, of which 45.0%, 28.9% and 13.5%, respectively were carbapenem-resistant (*3*). Based on historical resistance trends, projections indicate that by 2050, annual deaths attributable to antimicrobial resistance and deaths associated with antimicrobial resistance will increase to 1.91 million and 8.22 million, respectively, highly concentrated in low- and middle-income countries (*4*).

There is an unmet need for treatment options for priority pathogens that have antimicrobial resistance, especially for multidrug- and extensively drug-resistant gram-negative pathogens (*5*).

Summary of evidence: benefits

The application presented data on the benefits of imipenem + cilastatin + relebactam from randomized trials and real-world evidence from observational data.

Randomized trials

RESTORE-IMI 1 was a randomized, double-blind, multicentre, phase III trial that investigated the activity of imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) compared with colistin (300 mg loading dose, then 150 mg every 12 hours) plus imipenem + cilastatin (500 mg + 500 mg every 6 hours) for the treatment of complicated intra-abdominal and urinary tract infections and hospital-acquired pneumonia, including ventilator-associated pneumonia (6). The primary efficacy endpoint was favourable overall response, calculated on the microbiological modified intention-to-treat population (i.e. patients with a positive culture for an imipenem-resistant gram-negative pathogen who had received at least one dose of the study medicine) which included 21 and 10 patients in the intervention and comparator groups, respectively. The study was not powered to infer statistically significant differences in efficacy between treatment arms. A favourable overall response was reported in 15/21 (71.4%) and 7/10 (70.0%) patients in the intervention and comparator groups, respectively (adjusted difference −7.3%, 90% confidence interval (CI) −27.7% to 21.4%). Definitions of overall response differed by type of infection: for hospital-acquired pneumonia/ventilator-associated pneumonia, it was survival at day 28; for complicated intra-abdominal infections, it was clinical response at day 28; and for complicated urinary tract infections, it was clinical plus microbiological response 5–9 days after the end of therapy. A favourable clinical response at day 28 was reported in 15/21 (71.4%) and 4/10 (40.0%) patients in the intervention and comparator groups, respectively (adjusted difference 26.3%, 90% CI 1.3% to 51.5%). Among secondary endpoints, all-cause mortality at day 28 was lower in the intervention group (9.5% versus 30.0%; adjusted difference −17.3%, 90% CI −46.4% to 6.4%). Results by type of infection showed that for hospital-acquired pneumonia/ventilator-associated pneumonia 28-day survival was higher with imipenem + cilastatin + relebactam (87.5% versus 66.7%). None of the four patients with a complicated intra-abdominal infection had a favourable response at day 28. For complicated urinary tract infections, results for the primary efficacy endpoint favoured the comparator group (adjusted difference −27.3%, 90% CI −52.8% to 12.8%). The primary efficacy endpoint was met, indicating that imipenem + cilastatin + relebactam was at least as efficacious as colistin plus imipenem + cilastatin for the treatment of infections caused by imipenem-non-susceptible, colistin-susceptible gram-negative pathogens.

A secondary analysis of RESTORE-IMI1 data compared outcomes between the microbiological modified intent-to-treat (mMITT) and supplemental mMITT (SmMITT) populations, in which eligibility was based on local site testing ($n = 41$). Outcomes in the SmMITT population were consistent with those in the mMITT population (7).

RESTORE-IMI 2 was a randomized controlled, double-blind, multicentre, non-inferiority, phase III trial comparing imipenem + cilastatin + relebactam

(500 mg + 500 mg + 250 mg every 6 hours) with piperacillin + tazobactam (4 g + 500 mg every 6 hours) for the treatment of hospital-acquired pneumonia/ventilator-associated pneumonia in adults (*8*). Participants were randomized 1:1 to receive imipenem + cilastatin + relebactam ($n = 268$) or piperacillin + tazobactam ($n = 269$) for 7–14 days. The primary efficacy endpoint was all-cause mortality through day 28, while the key secondary endpoint was favourable clinical response at early follow-up (7–14 days after the end of treatment). Primary and secondary endpoints were evaluated in the modified intention-to-treat population, which excluded patients where only gram-positive cocci were isolated at baseline. Results for the primary endpoint of 28-day all-cause mortality showed lower mortality in the intervention group (15.9% versus 21.3%; adjusted difference −5.3%, 95% CI −11.9% to 1.2%). For favourable clinical response at early follow-up, results favoured the intervention group (61.0% versus 55.8%; adjusted difference 5.0%, 95% CI −3.2% to 13.2%). At day 28, a favourable clinical response was reported in 51.9% versus 50.6% of patients in the intervention and comparator groups, respectively (adjusted difference 1.1%, 95% CI −7.2% to 9.4%). The primary and secondary efficacy endpoints were met, indicating that imipenem + cilastatin + relebactam was at least as efficacious as piperacillin + tazobactam for the treatment of adults with hospital-acquired pneumonia/ventilator-associated pneumonia.

A randomized, double-blind, multicentre, non-inferiority, dose-ranging, phase II study compared the efficacy of relebactam 250 mg, relebactam 125 mg or placebo each given with imipenem 500 mg + cilastatin 500 mg for the treatment of 351 adult patients with complicated intra-abdominal infections irrespective of the type or susceptibility profile of the causative pathogen (*9*). The primary efficacy endpoint was favourable clinical response at discontinuation of therapy (5–9 days after end of treatment) and at late follow-up (28–42 days after end of treatment). With a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint. A similar study was conducted in adult patients with complicated urinary tract infections irrespective of the type or susceptibility profile of the causative pathogen (*10*). Again, with a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint of the proportion of patients who achieved a favourable microbiological response.

A randomized non-inferiority study compared imipenem + cilastatin +relebactam with standard of care gram-negative coverage (cefepime, piperacillin + tazobactam or meropenem) in 100 cancer patients with febrile neutropenia (*11*). Patients receiving imipenem + cilastatin + relebactam had a higher favourable clinical response at the end of intravenous therapy compared with

those receiving standard of care (90% versus 74%; $P = 0.042$). Responses between treatment groups were similar for test of cure at days 21–28, and late follow-up at days 35–74. Microbiological eradication responses were similar at all timepoints.

Observational studies

A 2024 retrospective, multicentre observational study described clinical characteristics and outcomes in 160 patients who received imipenem + cilastatin + relebactam for at least 2 days using data from a centralized database in the United States (*12*). Indications for antibacterial treatment during hospitalization included hospital-acquired or ventilator-associated bacterial pneumonia (53.8%) and complicated urinary tract infection (16.9%). Microbiology data were available for 37 patients, with the most commonly identified pathogens being *P. aeruginosa*, *Enterobacter cloacae* and *E. coli*. Multidrug-resistant *P. aeruginosa* was reported in 28/37 (75.7%) patients. Imipenem + cilastatin + relebactam was started a median of 8 days after hospital admission, and the median duration of treatment was 7 days. The all-cause in-hospital mortality rate overall was 24.4% and the 30-day mortality rate was 21.3%. In-hospital mortality was 57.6% and 15.7% among patients with and without coronavirus disease 2019 (COVID-19), respectively. Among patients with hospital-acquired or ventilator-associated bacterial pneumonia, the all-cause in-hospital mortality rate was 39.5%, which was higher than rates reported in the RESTORE-IMI 1 and RESTORE-IMI 2 trials and likely due to the inclusion of patients with COVID-19.

MIRAGE was a retrospective, multicentre, observational study describing the real-world effectiveness of imipenem + cilastatin + relebactam against multidrug-resistant *P. aeruginosa* pneumonia and bloodstream infections. Preliminary results have been published in abstract form (*13*). The study included patients who received imipenem + cilastatin + relebactam for more than 48 hours which was started within 7 days of first positive culture. Of 32 critically ill patients in the preliminary analysis, 72% and 53% achieved clinical success at day 7 and day 30, respectively. This was defined as survival, resolution of signs and symptoms of infection, and the absence of a recurrent infection due to multidrug-resistant *P. aeruginosa*. Rates of all-cause mortality at day 30 and day 90 were 22% and 31%, respectively.

A retrospective review of electronic health records reported treatment patterns of hospitalized patients with gram-negative infections treated with imipenem + cilastatin + relebactam in the United States. Results have been published in abstract form (*14*). Of 58 patient charts reviewed, the all-cause in-hospital mortality rate was 13.8%. Among the 25.9% of patients who experienced a 30-day hospital readmission after receiving imipenem + cilastatin + relebactam, two thirds had a single hospital readmission. In another retrospective observational study published in abstract form, patient characteristics, and the

effectiveness and safety of imipenem + cilastatin + relebactam were evaluated in 104 adult patients with infections due to *P. aeruginosa* (15). In more than 50% of patients, treatment was for lower respiratory-tract infections. Multidrug-resistant *P. aeruginosa* was isolated in 84.6% of patients. Clinical success was reported for 73.1% of patients, while the 30-day all-cause mortality was 16.3% Thirty-day microbiologic recurrence occurred in 14.4% of patients.

A retrospective case series described the outcomes in 21 adult patients with mixed infection sources (52% were pulmonary infections) who were treated with imipenem + cilastatin + relebactam (16). Most infections were caused by *P. aeruginosa* (76%), of which all except one were multidrug-resistant. The 30-day all-cause mortality rate was 33%, and clinical cure rate was 62%. Results from an extension of this study were presented as a conference poster in 2023; the study reported a 30-day all-cause mortality rate of 15.4% (17).

In vitro studies

Data from an in vitro study which assessed the antimicrobial activity of imipenem + cilastatin + relebactam and aztreonam alone and in combination against 10 well characterized *P. aeruginosa* isolates (three parent and seven metallo-β-lactamase producers) demonstrated synergy in five of the strains and restoration of aztreonam activity in the remaining five when combination treatment was used (18).

Among multidrug-resistant *P. aeruginosa* isolates collected before and after treatment-emergent resistance to ceftolozane + tazobactam, whole genome sequencing identified treatment-emergent mutations in ampC in 79% (11/14) of paired isolates. AmpC mutations were associated with cross-resistance to ceftazidime + avibactam but increased or maintained susceptibility to imipenem + cilastatin + relebactam. A high percentage (81%) of isolates resistant to ceftolozane + tazobactam were susceptible to imipenem + relebactam (19). A second assessment found that imipenem + cilastatin + relebactam retained activity against 70–75% of cephalosporin-resistant *P. aeruginosa* isolates resistant to ceftolozane + tazobactam, ceftazidime + avibactam and meropenem + vaborbactam (20).

Summary of evidence: harms

In RESTORE-IMI 1, the incidence of ≥1 adverse events, serious adverse events, serious drug-related adverse events and treatment discontinuations due to adverse events was lower in patients who received imipenem + cilastatin + relebactam than in patients who received colistin plus imipenem + cilastatin, although the trial was not powered to detect statistical significance in these outcomes. A statistically significant lower incidence of treatment-emergent nephrotoxicity was found in patients who received imipenem + cilastatin + relebactam than in patients who received colistin plus imipenem + cilastatin (10.3% versus 56.3%; $P = 0.002$) (6).

In an additional analysis of RESTORE-IMI 1, nephrotoxicity was retrospectively evaluated using two acute kidney injury assessment criteria (kidney disease improving global outcomes (KDIGO) and risk, injury, failure, loss and end-stage kidney disease (RIFLE)). The analysis found that, based on KDIGO and RIFLE criteria, imipenem + cilastatin + relebactam had a more favourable renal safety profile than colistin-based therapy in patients with serious gram-negative bacterial infections not susceptible to imipenem (*21*).

In RESTORE-IMI 2, the incidence of ≥ 1 adverse events, deaths, serious adverse events, drug-related adverse events and treatment discontinuations due to adverse events were comparable between treatment groups (*8*). A secondary analysis of RESTORE-IMI 2 observed that emergence of non-susceptibility to imipenem + cilastatin + relebactam occurred rarely. Emergence of non-susceptibility to imipenem + cilastatin + relebactam was identified by isolates that were susceptible at baseline but subsequently were identified during treatment and tested non-susceptible. Of all randomized participants who received imipenem + cilastatin + relebactam, 5/268 (1.9%) and 2/268 (0.7%) had non-susceptible post-baseline isolates by Clinical and Laboratory Standards Institute criteria and European Committee on Antimicrobial Susceptibility Testing criteria, respectively (*22*).

In the dose-ranging phase II studies in patients with complicated intra-abdominal infections (*9*) and complicated urinary tract infections (*10*), imipenem + cilastatin + relebactam had a comparable safety profile to imipenem + cilastatin monotherapy, with similar rates of adverse events, serious adverse events and drug-related adverse events between each group and between different doses of relebactam.

Additional evidence

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WHO guidelines

WHO guidelines for the use of imipenem + cilastatin + relebactam are not currently available.

Costs/cost–effectiveness

The application presented global cost–effectiveness and budgetary impact analyses from the United States payer perspective.

Cost–effectiveness of imipenem + cilastatin + relebactam versus colistin plus imipenem for the treatment of infection(s) caused by confirmed carbapenem-non-susceptible pathogens was examined (*23*). The analysis comprised a decision-tree depicting initial hospitalization and a Markov model projecting long-term health and economic impacts following discharge. The decision tree,

informed by clinical data from RESTORE-IMI 1 trial, modelled clinical outcomes (mortality, cure rate and adverse events including nephrotoxicity) in the two comparison scenarios of imipenem + cilastatin + relebactam versus colistin plus imipenem for patients with carbapenem-non-susceptible gram-negative infection. Subsequently, a Markov model translated these hospitalization stage outcomes (i.e. death or uncured infection) to long-term consequences such as quality-adjusted life years (QALYs). Sensitivity analyses were conducted to test the model's robustness.

Imipenem + cilastatin + relebactam compared to colistin plus imipenem demonstrated a higher cure rate (79.0% versus 52.0%), lower mortality (15.2% versus 39.0%) and reduced nephrotoxicity (14.6% versus 56.4%). On average, a patient treated with imipenem + cilastatin + relebactam gained an additional 3.7 QALYs over a lifetime. Higher drug acquisition costs for imipenem + cilastatin + relebactam were offset by shorter length of hospital stay and lower costs related to adverse events, which resulted in net savings of 11 015 United States dollars (US$) per patient. Sensitivity analyses suggested that imipenem + cilastatin + relebactam had a high likelihood of being cost-effective at a United States willingness-to-pay threshold of US$ 100 000 to US$ 150 000 per QALY.

The cost–effectiveness of imipenem + cilastatin + relebactam versus piperacillin + tazobactam for the treatment of health-care-acquired and ventilator-associated bacterial pneumonia was examined (*24*). An economic model comprising of a decision-tree depicting initial hospitalization and a Markov model projecting long-term health and economic impacts following discharge was developed. Efficacy data to determine clinical outcomes in the short-term decision tree were taken from the modified intent-to-treat population of RESTORE-IMI 2. Hospitalization costs were modelled using the average observed length of stay as reported in RESTORE-IMI 2, and unit costs for intensive care units and general wards (US$ 5743 and US$ 2694 per day, respectively) were sourced from the literature. Total costs in both arms were primarily driven by hospitalization costs in the short term. Costs of resources use, adverse event and monitoring were comparable across treatment arms, with incremental costs for imipenem + cilastatin + relebactam primarily being driven by increased treatment acquisition costs. The resulting incremental cost–effectiveness ratio was US$ 14 053 per QALY gained, well below the typical United States willingness-to-pay threshold of US$ 100 000 per QALY gained.

Availability

As of October 2024, imipenem + cilastatin + relebactam has regulatory approval 51 countries and market availability in 33 countries. It is not currently included on national essential medicines lists.

Other considerations

The WHO Technical Advisory Group on AWaRe (TAG-AWaRe) reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML. Comments from the TAG-AWaRe highlighted:

- infections due to multidrug-resistant organisms, particularly high-priority carbapenem-resistant Enterobacterales, *Pseudomonas* and *Acinetobacter* species continue to be associated with considerable morbidity and mortality globally;
- access to essential Reserve antibiotics is still limited in many settings;
- limited clinical trial data suggest imipenem + cilastatin + relebactam has similar clinical efficacy and a more favourable safety profile than the combination of imipenem and colistin for treatment of complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia;
- small observational studies conducted in the United States, in which most patients had infections caused by difficult-to-treat resistant *Pseudomonas* species and a minority had infections caused by *K. pneumoniae* carbapenemase--producing carbapenem-resistant Enterobacterales, demonstrated a clinical success rate of about 70%, but with documented recurrent infections and development of resistance;
- imipenem + cilastatin + relebactam may play a role as an additional therapeutic option in countries where *K. pneumoniae* carbapenemase-producing carbapenem-resistant Enterobacterales and difficult-to-treat resistant *Pseudomonas* species are prevalent. However, other carbapenemases against which imipenem + cilastatin + relebactam is not active are more prevalent than KPC in many countries.
- concern for price, access and potential inappropriate use due to limited capacity for microbiological diagnosis and surveillance (including genotyping) and limited implementation of antimicrobial stewardship policies and interventions, particularly in low- and middle-income countries.

Committee recommendations

The Expert Committee acknowledged that antimicrobial resistance remains a critical global health threat, disproportionately affecting low- and middle-income countries. The Committee recognized the increasing mortality associated with carbapenem-resistant gram-negative bacterial infections. The

Committee noted that imipenem + cilastatin + relebactam has in vitro activity against most carbapenemase-producing Enterobacterales, excluding metallo-beta-lactamase producers and OXA-48-like enzymes. The Committee also noted that imipenem + cilastatin + relebactam has in vitro activity against *P. aeruginosa*, including some isolates resistant to other beta-lactam/beta-lactamase inhibitor combinations.

The Committee recalled the decision of the 2023 Expert Committee not to recommend the inclusion of imipenem + cilastatin + relebactam on the EML due to its lack of in vitro activity against metallo-beta-lactamase-producing carbapenemase-producing Enterobacterales, the inclusion of other Reserve antibiotics with a similar mechanism of action and spectrum of activity on the EML, limited clinical evidence and high price.

In consideration of the clinical evidence presented in the current application, the Committee noted that no new randomized trials to those presented in the previous application were available. The Committee noted new evidence from observational studies and acknowledged the potential role of imipenem + cilastatin + relebactam in treating multidrug-resistant and extensively drug-resistant *P. aeruginosa* infections. However, the Committee noted that these studies were small, all conducted in the United States and most were published only as conference abstracts. Therefore, the Committee concluded that high-quality clinical data for imipenem + cilastatin + relebactam remained limited.

The Committee appreciated and considered the reviews of the application by the TAG-AWaRe and the WHO technical unit, noting the different conclusions.

Overall, the Committee concluded that there was insufficient new high-quality evidence to justify revising the 2023 Expert Committee's conclusions.

Therefore, the Expert Committee did not recommended the inclusion of imipenem + cilastatin + relebactam for the treatment of infections caused by multidrug-resistant organisms for the same reasons as given by the previous Expert Committee: imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally, other Reserve antibiotics with a similar spectrum of activity are already included on the Model Lists.

The Committee advised that future evaluation of an application for inclusion of imipenem + cilastatin + relebactam on the Model List could be considered following any changes to the definition of the AWaRe Reserve category arising from the planned revision of AWaRe definitions.

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6.2.5 Antituberculosis medicines

Rifapentine – new formulation – EMLc

Rifapentine	ATC code: J04AB05

Proposal

Addition of rifapentine 150 mg dispersible, scored tablets to the core list of the EMLc for use as part of tuberculosis preventive treatment in children.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Tablet (dispersible, scored): 150 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Rifapentine was added to the core list of the EML and EMLc in 2015 for treatment, in combination with isoniazid, of latent tuberculosis infection (now known as tuberculosis preventive treatment) (*1*). Currently listed rifapentine formulations are 150 mg and 300 mg conventional tablets.

Rifapentine is used for tuberculosis preventive treatment in combination with isoniazid as a weekly regimen for 3 months or a daily regimen for 1 month (*2*).

Public health relevance

Globally, an estimated 10.8 million people fell ill with tuberculosis in 2023. The disease caused an estimated 1.25 million deaths, including 161 000 deaths from tuberculosis in people with human immunodeficiency virus (HIV) (*3*).

The estimated incidence of tuberculosis in children and young adolescents younger than 15 years is 1.25 million a year – 12% of the total incidence. Children younger than 5 years make up 47% of the incidence in this age group. Tuberculosis-related deaths in children and young adolescents constitute 15% of total mortality due to the disease (*3*).

Summary of evidence: benefits

Evidence for the benefits of rifapentine was evaluated in 2015 when rifapentine was first considered for inclusion on the Model Lists. The application stated that the effectiveness of the proposed dispersible tablet formulation is not expected to differ from conventional rifapentine formulations provided it is quality-assured with proven bioavailability.

The application referred to preliminary data from the Tuberculosis Trials Consortium (TBTC) Study 35 (*4*), a phase I/II dose-finding and safety study of rifapentine (given as water-dispersible monolayer and/or fixed dose combination with isoniazid) in HIV-positive and HIV-negative children with latent tuberculosis infection aged 0–12 years. A total of 64 children were enrolled in four age cohorts (cohort 1: ≥ 4 to ≤ 12 years; cohort 2: ≥ 24 months to < 4 years; cohort 3: ≥ 12 to < 24 months; and cohort 4: 0 to < 12 months) at the time of the analysis. The age range of the participants was 3.4 weeks to 12.9 years; 33 were < 2 years, 17 < 1 year and five ≤ 3 months. Seven children with HIV who were receiving once daily dolutegravir were also included. Children with or without HIV received 12 weekly doses of rifapentine and isoniazid under direct observation. Intensive pharmacokinetic sampling was conducted after the first dose and some sampling after the 12th dose. An interim analysis was conducted of at least six participants in cohorts 1 and 2 for whom pharmacokinetic and safety data were available. Following the first interim analysis, cohorts 3 and 4 were enrolled at doses based on the modelled pharmacokinetic data obtained from children in cohorts 1 and 2. After a second interim analysis, the rifapentine doses for children < 2 years were adjusted according to the interim analyses of cohorts 3 and 4. The aim was to achieve pharmacokinetic targets derived from the TBTC Study 26 of adult exposures and safety targets, with no more than one grade 3 or higher adverse event related, possibly or definitely, to the study drug (either rifapentine or isoniazid) in each of the mini-cohorts in the interim analyses. The overall exposure to rifapentine with the doses administered in TBTC Study 35 were aligned closely with adult rifapentine pharmacokinetic targets for all weight

bands, except in those of infants aged < 3 months, of whom those weighing 3–4 kg and 5–6 kg were exposed to higher doses than the target (5). The results of this study informed updated WHO dosing guidance for tuberculosis preventive treatment with rifapentine and isoniazid (6).

Summary of evidence: harms

Evidence of the harms of rifapentine was evaluated in 2015 when rifapentine was first considered for inclusion on the Model Lists.

The doses prescribed in TBTC Study 35 were based only on weight and were well tolerated, with no notable safety concerns observed during the study (5).

Additional evidence

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WHO guidelines

Recommendations in current WHO guidelines for tuberculosis preventive treatment in patients regardless of HIV status are summarized below (2).

- 6- or 9-month regimen of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin (strong recommendation, moderate-to-high-certainty evidence).
- 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin (conditional recommendation, low to moderate-certainty evidence).

Costs/cost–effectiveness

Rifapentine 150 mg scored, dispersible tablets are included in the Stop TB Partnership's global drug facility catalogue at a price of 13.80 United States dollars (US$) per 100 tablets. At this price, the 3-month regimen of weekly rifapentine plus isoniazid for children is cheaper than alternative regimens. For example, for a child weighing 15 kg, the cost of this regimen is US$ 6.53 compared to US$ 14.18 for the 3-month regimen of isoniazid and rifampicin or US$ 16.20 for the 6-month isoniazid regimen (7).

Availability

Rifapentine 150 mg dispersible tablets manufactured by Lupin Limited were prequalified by WHO in November 2024. A second manufacturer has started development.

Rifapentine 150 mg scored, dispersible tablet formulation is available from the Stop TB Partnership's global drug facility. This formulation is also

available through an Early Market Access Vehicle of about 85 000 patient courses of rifapentine promoted by the UNITAID-funded IMPAACT4TB consortium to catalyse the uptake of the paediatric product (*8*).

Other considerations

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Committee recommendations

The Expert Committee recognized that age-appropriate, child-friendly formulations of medicines for the treatment of tuberculosis, when available and quality-assured, are essential public health interventions to meet the needs of paediatric patients.

The Committee noted that currently listed rifapentine formulations for tuberculosis preventive treatment on the EMLc are 150 mg and 300 mg conventional tablets, which may not be acceptable for paediatric patients unable to swallow solid dosage forms. The 150 mg dispersible tablet rifapentine formulation is prequalified by WHO and is available through the Stop TB Partnership global drug facility.

Based on these considerations, the Expert Committee recommended the addition of rifapentine 150 mg dispersible tablets to the core list of the EMLc for tuberculosis preventive treatment in accordance with recommendations in WHO guidelines.

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6.4 Antiviral medicines

6.4.2.5 Fixed-dose combinations of antiretroviral medicines

Abacavir + dolutegravir + lamivudine – addition – EMLc

Abacavir + dolutegravir + lamivudine **ATC code: J05AR13**

Proposal

Addition of abacavir + dolutegravir + lamivudine to the core list of the EMLc for the treatment of HIV-1 infection in paediatric patients at least 4 weeks of age and weighing at least 3 kg.

Applicant

Clinton Health Access Initiative, Inc., Boston, MA, United States of America

WHO technical department

Global HIV, Hepatitis and STI Programme

EML/EMLc

EMLc

Section

6.4.2.5 Fixed-dose combinations of antiretroviral medicines

Dose form(s) & strengths(s)

Tablet (dispersible): 60 mg + 5 mg + 30 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

A triple fixed dose combination of abacavir + dolutegravir + lamivudine has not been previously considered for inclusion on the EMLc. Currently, the component medicines are all individually included on the EMLc as individual medicines (dolutegravir, lamivudine) or dual fixed dose combinations (abacavir + lamivudine).

Public health relevance

According to the 2024 Global AIDS Update by UNAIDS, in 2023, nearly 40 million people were living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) worldwide, with 1.3 million new HIV-1 infections reported (a decrease of 39% since 2010) and 630 000 HIV-related deaths. An estimated 1.4 million children aged 0–14 years were living with HIV, with 86% residing in sub-Saharan Africa. Despite a reduction in mother-to-child transmission of HIV in recent years, 120 000 new paediatric infections occurred in 2023 and 76 000 children died from AIDS-related causes (*1*).

In the absence of antiretroviral treatment, over 50% of HIV-infected infants progress to AIDS or death by the age of 2 years (*2*). Despite recognition of the advantages of early treatment, paediatric treatment coverage still reached only 57% of children eligible for treatment in 2023 and only 48% of all children living with HIV have viral suppression, substantially fewer than the 78% of adults living with HIV (*1*).

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral treatment has been widely used in paediatric patients for both prevention of transmission and treatment. A 2017 survey of newly diagnosed children in five sub-Saharan African countries indicated resistance to one or more NNRTIs in up to 53% of the cohort (*3*). These increasing rates of resistance to the previously recommended first-line treatments prompted WHO to recommend rapid transition to dolutegravir-based treatment in 2018 as child-friendly formulations become available.

Summary of evidence: benefits

In 2017, the Paediatric Antiviral Drug Optimization-3 working group meeting, convened by WHO, reviewed available data and recommended the development of a triple fixed-dose combination of abacavir + dolutegravir + lamivudine in a dispersible tablet formulation (*4*). Paediatric data used to inform this recommendation came from the IMPAACT P1093 and ODYSSEY clinical trials.

IMPAACT P1093 was a phase I/II single-arm, open-label trial to assess the pharmacokinetics safety and efficacy of dolutegravir plus an optimized background regimen in HIV-infected children and adolescents (*5*–*7*). Data from the P1093 trial included: cohorts 1 (aged 12 to < 18 years) and 2 (6 to < 12 years), which provided evidence supporting the use of dolutegravir 50 mg film-coated tablets in paediatric patients weighing more than 14 kg; and cohorts 3 (2 to < 6 years), 4 (6 months to < 2 years) and 5 (4 weeks to < 6 months), which provided evidence supporting the use of dolutegravir 25 mg dispersible tablets. Seventy-five study participants ranging in age from 1 month to 18 years received the currently approved dose (determined by weight and age) of dolutegravir film-

coated tablets or dispersible tablets. Eighty percent of participants were treatment-experienced, but none had received integrase strand transfer inhibitor. Among the 75 participants, 42 received dolutegravir for at least 48 weeks. At week 48, 69% of participants achieved HIV RNA < 50 copies/mL and 79% achieved HIV RNA < 400 copies/mL. The median CD4 count (per cent) increase from baseline to week 48 was 141 cells/mm3 (7%). The effectiveness observed in the trial was comparable to that of treatment-experienced adult subjects.

ODYSSEY was an open-label, randomized, non-inferiority trial that compared the efficacy and safety of dolutegravir-based antiretroviral treatment with standard care in 707 children and adolescents aged < 18 years and weighing at least 14 kg starting first- or second-line treatment (8). Participants were randomly assigned to receive dolutegravir-based antiretroviral treatment ($n = 350$ of whom 154 started dolutegravir as first-line therapy and 196 as second-line therapy or the local standard treatment ($n = 357$). Of the first-line treatment participants, 92% received efavirenz and of the second-line treatment participants, 98% received a boosted protease inhibitor. Across all arms, 65% of participants received abacavir + lamivudine as the nucleoside reverse transcriptase inhibitor backbone. The primary endpoint was the proportion of participants with virological or clinical treatment failure by 96 weeks. By 96 weeks, 47 participants in the dolutegravir group and 75 in the standard-care group experienced treatment failure (adjusted hazard ratio (HR) 0.60, 95% confidence interval (CI) 0.42 to 0.86). Treatment effects were similar between first- and second-line cohorts. Of the participants in whom first-line dolutegravir therapy failed, none had a major dolutegravir-related resistance mutation, whereas 29 participants in whom the standard care failed developed non-nucleoside reverse transcriptase inhibitor and/or nucleoside reverse transcriptase inhibitor resistance mutations. The study concluded that dolutegravir-based antiretroviral therapy was superior to standard care in children and adolescents with HIV-1 infection starting first- or second-line treatment.

IMPAACT 2019 was a phase I/II, open-label, single-arm dose-confirmation study that evaluated the pharmacokinetics, safety and tolerability of a fixed-dose combination formulations (immediate-release or dispersible tablets) of abacavir + dolutegravir + lamivudine (9). Fifty-seven infants and children younger than 12 years and weighing 6 kg to < 40 kg were enrolled, 54 of whom were treatment-experienced. Participants weighing < 25 kg received the dispersible tablet formulation (60 mg + 5 mg + 30 mg) and participants weighing 25 kg to < 40 kg received the immediate-release tablet formulation (600 mg + 50 mg + 300 mg). The primary pharmacokinetic outcome measures were the geometric mean area under the concentration time curve over the 24-hour dosing interval, maximum concentration and concentration at 24 hours post-dose for dolutegravir, abacavir, and lamivudine for each of five weight-bands. Overall, pharmacokinetic targets were achieved in all weight bands confirming the selected doses through 24

weeks of dosing. After 24 weeks, all treatment-experienced participants and 2/3 treatment-naïve participants had virological suppression. The study concluded that dosing of abacavir, dolutegravir and lamivudine was confirmed in children weighing 6 kg < 40 kg, and both formulations were safe, well tolerated and efficacious through 24 weeks of treatment.

Summary of evidence: harms

In the IMPAACT 2019 study, the safety profile was comparable to that observed in adults and both formulations were well tolerated by paediatric patients In the ODYSSEY trial, similar rates of grade 3 or 4 adverse events and serious adverse events occurred in participants receiving either dolutegravir or standard care. Participants receiving dolutegravir-based treatment were observed to have slightly increased weight, height and body mass index for age compared with those receiving standard care, which was attributed to improvement in normal growth as weight and height both increased. Overall adherence, acceptability and palatability were considered favourable. Both formulations were well tolerated and there were no grade 3 or higher adverse events related to abacavir + dolutegravir + lamivudine and no discontinuation of treatment due to adverse events (*9*).

Additional evidence

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WHO guidelines

The 2021 WHO consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring recommend a regimen of dolutegravir in combination with an nucleoside reverse transcriptase inhibitor backbone of abacavir and lamivudine as the preferred first-line treatment for infants and children with HIV older than 4 weeks and weighing at least 3 kg (conditional recommendation, low-certainty evidence) (*10*).

Costs/cost–effectiveness

No cost–effectiveness studies for abacavir + lamivudine + dolutegravir dispersible tablets were identified in the application.

The Clinton Health Access Initiative and Unitaid have negotiated ceiling prices with Aurobindo and Mylan/Viatris of 15 United States dollars (US$) ex-works per 180-count pack of abacavir + dolutegravir + lamivudine dispersible tablets. These prices are available to all public-sector procurers buying for countries included in the relevant Medicines Patent Pool licenses.

In almost all low- and middle-income settings where abacavir + dolutegravir + lamivudine dispersible tablets would be accessed, governments and donors pay for antiretroviral treatments in public facilities so there are no costs

to patients. The estimated per person per year costs of abacavir + dolutegravir + lamivudine dispersible tablets and comparator regimens are presented in Table 7. Although abacavir + dolutegravir + lamivudine dispersible tablets represents a slight increase in per person per year costs compared with separate abacavir + lamivudine and dolutegravir dispersible tablets, it is anticipated that the price of abacavir + dolutegravir + lamivudine dispersible tablets will decrease as volumes increase. Additionally, abacavir + dolutegravir + lamivudine dispersible tablets are expected to bring cost savings from warehousing and freight efficiencies due to fewer bottles required per patient, reducing transportation and storage costs.

Table 7

Estimated per person per year cost (ex-works in US$) of abacavir + dolutegravir + lamivudine dispersible tablets and comparator regimens by weight band

Regimen (no. of tablets)	Cost, US$		
	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg
ABC 60 mg + DTG 5 mg + 3TC 30 mg (180)	89.10	118.80	145.85
ABC 120 mg + 60 mg (30) and DTG 10 mg (90)	72.60	96.80	121.00
ABC 120 mg + 3TC 60 mg (30) and LPV/r 40/10 mg (120)	352.80	470.40	588.00

ABC: abacavir; DTG: dolutegravir; LPV/r: lopinavir + ritonavir; 3TC: lamivudine; US$: United States dollars.

Availability

The innovator product, TRIUMEQ PD (ViiV Healthcare), has received regulatory approval for the treatment of HIV in children at least 3 months of age and weighing at least 6 kg in several major markets, including Chile, European Union, Switzerland, United Kingdom of Great Britain and Northern Ireland, and the United States. Generic versions are available from at least three generic manufacturers, two of which are currently prequalified by WHO. Generic versions are being procured and introduced in low- and middle-income countries through licensing agreements between ViiV Healthcare and the Medicines Patent Pool. These agreements facilitate access to affordable generic versions of abacavir + dolutegravir + lamivudine dispersible tablets in 120 countries included in the licence. Additionally, there are nine more countries outside the licenced territory where no patents have been found, potentially allowing Medicines Patent Pool sublicencees to supply these markets.

Other considerations

Based on the WHO paediatric quality product profile assessment tool, this formulation was determined to be appropriate for the ages and weights indicated (older than 4 weeks and weighing more than 6 kg). The dispersible tablet formulation is particularly beneficial for young children who may have difficulty swallowing solid dosage forms. This age-appropriate formulation supports adherence and effective treatment outcomes in paediatric populations.

Committee recommendations

The Expert Committee recognized that age-appropriate, child-friendly formulations of antiretroviral medicines, when available and quality-assured, are essential public health interventions to meet the needs of paediatric patients with HIV.

The Committee recalled the recommendations of previous Expert Committees to include the component medicines of the proposed fixed-dose combination in the EMLc based on favourable benefits and acceptable safety and public health need for paediatric patients. The Committee noted that new data from the IMPAACT 2019 trial indicated the achievement of pharmacokinetic targets of the proposed formulation across paediatric weight bands.

The Committee also noted that a combination regimen of abacavir + dolutegravir + lamivudine was the preferred first-line treatment for infants and children recommended in WHO guidelines and considered that the availability of a dispersible tablet formulation supported the implementation of these guidelines by providing a simplified, age-appropriate treatment option.

The Committee appreciated that the proposed formulation was the subject of licensing agreements with the Medicines Patent Pool, supporting affordable access in low- and middle-income countries, and that generic versions were already available and prequalified by WHO.

Based on these considerations, the Expert Committee recommended the addition of abacavir + dolutegravir + lamivudine dispersible tablets to the core list of the EMLc for the treatment of paediatric patients with HIV, with use in accordance with recommendations in WHO guidelines.

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6.4.3 Other antivirals

Ribavirin – deletion – EMLc

Ribavirin **ATC code: J05AP01**

Proposal

Deletion of ribavirin for the treatment of viral haemorrhagic fevers from the EML and EMLc.

Applicant

Alejandro Costa, WHO Viral Haemorrhagic Fever Team

WHO technical department

Department of Epidemic and Pandemic Threat Management

EML/EMLc

EML and EMLc

Section

6.4.3 Other antivirals

Dose form(s) & strengths(s)

Injection: 800 mg, 1 g in 10 mL phosphate buffer solution

Solid oral dosage form: 200 mg, 400 mg, 600 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Ribavirin has been included on the EML and EMLc for use in the treatment of viral haemorrhagic fevers since 2007.

Ribavirin is also included on the EML for use in combination with direct-acting antiviral agents in the treatment of hepatitis C virus infection.

Public health relevance

Lassa fever is an acute viral illness caused by the Lassa virus. It is endemic in Benin, Ghana, Guinea, Liberia, Mali, Nigeria and Sierra Leone, and likely also exists in

other west African countries. The overall case fatality rate is 1% but may be 15% or higher among hospitalized patients with severe disease. While ribavirin has been used for Lassa fever, there is now considerable uncertainty about its efficacy and safety for this indication. Early intensive supportive care, including fluid management and treatment of specific symptoms, can improve survival (*1*).

Crimean–Congo haemorrhagic fever virus is a cause of severe viral haemorrhagic fever outbreaks that have a case fatality rate of up to 40%. Crimean–Congo haemorrhagic fever is endemic in Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north. Ribavirin has been used as an off-label treatment but there is considerable uncertainty about its efficacy, given the lack of clinical evidence, and its optimal dosing regimens (*2*).

Summary of evidence: benefits

The justification for the use of ribavirin in the treatment of Lassa fever was mainly based on a quasi-experimental study (divided in two phases) conducted in the 1980s that evaluated the efficacy of ribavirin and Lassa virus–convalescent plasma for the treatment of Lassa fever (*3*). This study concluded that ribavirin was effective in treating Lassa fever patients based on reduced case fatality rates in patients treated with ribavirin. However, the evidence has been found to be associated with a substantial risk of bias due to the use of historic controls, non-randomized allocation of treatment, heterogenous use of Lassa virus laboratory diagnostic assays and small number of patients. In addition, data from this study suggest a potentially harmful effect in patients with aspartate aminotransferase levels lower than 150 IU/mL and in patients with suspected Lassa fever but without laboratory confirmation. The efficacy and safety of ribavirin has not been further established in appropriate randomized controlled trials.

A 2018 Cochrane systematic review of five studies (one randomized controlled trial and four non-randomized studies, 612 participants) evaluated the effects of ribavirin in the treatment of Crimean–Congo haemorrhagic fever (*4*). Due to insufficient data and a high risk of bias in the non-randomized studies, the authors were unable to determine whether ribavirin reduced mortality, length of hospital stay and risk of needing platelet transfusions, or whether ribavirin was associated with an increased risk of adverse effects.

A 2022 systematic review of 13 studies published between 1986 and 2020 evaluated the comparative effectiveness of ribavirin versus no ribavirin treatment on mortality outcomes in patients with Lassa fever (*5*). Although ribavirin was associated with decreased mortality rates in most studies, these studies were found to be at a critical or serious risk of bias, which undermined the reliability of the findings.

A 2019 systematic review and meta-analysis of five retrospective cohort studies and one prospective clinical trial evaluated the efficacy of intravenous

ribavirin for the treatment of Lassa fever (*6*). From the pooled analysis of the retrospective studies, ribavirin was associated with reduced odds of death (odds ratio (OR) 0.13, 95% confidence interval (CI) 0.04 to 0.40; very-low-certainty evidence). However, the included studies had a critical risk of bias due to the allocation processes and were thought to overestimate the treatment effect. From the prospective trial, there was very-low-certainty evidence that ribavirin was associated with reduced mortality in patients with elevated aspartate aminotransferase levels (OR 0.41, 95% CI 0.23 to 0.73), but increased mortality in patients without elevated aspartate aminotransferase levels (OR 2.37, 95% CI 1.07 to 5.25). This trial was considered to have a critical risk of bias due to missing data, participant misclassification, and unreliable randomization and treatment allocation procedures.

Summary of evidence: harms

Ribavirin may be harmful to patients with mild forms of Lassa fever (*7*). Higher doses than recommended have been associated with hypocalcaemia and hypomagnesaemia. A theoretical reproductive risk in humans exists due to teratogenic effects observed in animals.

Additional evidence

A 2023 systematic review assessed the availability, scope, standardization and quality of clinical management guidelines for viral haemorrhagic fever (*8*). The review identified 32 guidelines on viral haemorrhagic fevers, focusing on their quality and evidence. Of these guidelines, 25 (78%) were of low quality and lacked supporting evidence. Only eight guidelines (25%) had been produced or updated in the past 3 years. The guidance on supportive care and therapeutics was often sparse and sometimes contradictory. The authors concluded that guidelines based on uncertain evidence are detrimental to patient care and clinical practice. They emphasized the need for investments in trials to identify optimal treatment strategies for viral haemorrhagic fevers and prioritization of affordable and scalable interventions to improve global health outcomes.

WHO guidelines

WHO guidance for the clinical management of patients with viral haemorrhagic fevers is currently under review.

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

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Committee recommendations

The Expert Committee noted that the justification to use ribavirin for viral haemorrhagic fevers is based on one biased quasi-experimental study from the 1980s. However, the efficacy and safety of ribavirin have not been verified in appropriate follow-up randomized trials. Recent systematic reviews concluded that the available evidence was insufficient to recommend the routine use of ribavirin in Crimean–Congo haemorrhagic fever or Lassa fever given the high risk of bias in the included studies.

Additional concerns over the lack of effect of ribavirin for viral haemorrhagic fever emerged. A biological rationale is lacking to support the use of ribavirin in this infection given that its mechanism of action is unknown. Further, evidence points to a potentially harmful effect in patients with mild disease.

Based on these considerations, and until the efficacy and safety of ribavirin is verified in further research, the Expert Committee recommended the deletion of ribavirin for the treatment of viral haemorrhagic fevers from the EML and EMLc.

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6.5 Antiprotozoal medicines

6.5.5.1 African trypanosomiasis

Fexinidazole – new indication – EML and EMLc

Fexinidazole **ATC code: P01CA03**

Proposal

Extension of the indications for the listing of fexinidazole on the EML and EMLc to include treatment of first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* in adults and children (aged ≥ 6 years and weighing ≥ 20 kg).

Applicant

Sanofi Winthrop Industrie, Gentilly, France

WHO technical department

The Department of Control of Neglected Tropical Diseases reviewed the application and indicated its support for the inclusion of fexinidazole on the Model Lists for the new indication of African trypanosomiasis due to *Trypanosoma brucei rhodesiense*.

EML/EMLc

EML and EMLc

Section

6.5.5.1 African trypanosomiasis

Dose form(s) & strengths(s)

Tablet: 600 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Fexinidazole has not previously been evaluated for inclusion on the Model Lists for the treatment of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* (r-HAT). Fexinidazole was included in 2019 for treatment of first-

stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis due to *Trypanosoma brucei gambiense* (g-HAT) in adults and children.

The Model Lists currently include suramin sodium and melarsoprol for treatment of first- and second-stage r-HAT, respectively.

Public health relevance

Human African trypanosomiasis, or sleeping sickness, is one of the most neglected tropical diseases. Without diagnosis and treatment, it is usually fatal as the parasites multiply in the body, cross the blood–brain barrier and invade the central nervous system at the late stage of the disease. Human African trypanosomiasis takes two forms, depending on the parasite involved: *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*.

r-HAT is a rare disease that contributes to a small proportion of cases of human African trypanosomiasis (about 1.5% (110/7201) in 2012 and about 3.4% (24/699) in 2023) (1, 2). r-HAT is an acute and aggressive form of human African trypanosomiasis, as the first symptoms appear within 1 to 3 weeks and the progression from the first to second stage occurs within 3 to 8 weeks. If left untreated, r-HAT patients generally suffer from central nervous system impairment and usually die within 4 to 6 months from cardiac failure and cardiac arrest (3, 4).

r-HAT and g-HAT differ in most of their characteristics (3, 5). r-HAT is a zoonotic disease with humans being accidental hosts, while humans are the primary hosts for g-HAT. *T. b. rhodesiense* parasites are transmitted by tsetse flies of the *Glossina morsitans* species. This species lives in drier and more open areas of woodlands and savannahs than the tsetse flies of the *Glossina palpalis* group that live in riverine and forest areas and which transmit g-HAT parasites (6). Wildlife and domestic animals (mainly cattle) are the animal reservoirs of *T. b. rhodesiense* parasites (7). Encroachment into wildlife areas and the increasing density of livestock and humans are key factors that sustain trypanosome transmission (8).

In contrast to g-HAT diagnosis, no serological field diagnostic tests are available for r-HAT, which depends on the microscopic detection of parasites mainly in blood and cerebrospinal fluid from suspected clinical cases. Both *T. b. rhodesiense* and *T. b. gambiense* trypanosomes can only be distinguished from each other by molecular biological tests which are not available in most African health facilities with HAT expertise (9). Trypanosome distinction therefore relies on the specific geographical distribution of each subspecies: *T. b. rhodesiense* in east and south-eastern Africa (e.g. Ethiopia, Kenya, Malawi, southern Uganda, United Republic of Tanzania, Zambia and Zimbabwe) and *T. b. gambiense* in west and central Africa (e.g. Angola, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Guinea, South Sudan and north-eastern Uganda) (1–3).

Summary of evidence: benefits

Evidence for the efficacy of fexinidazole in patients with r-HAT is based on data from one (yet to be published) single-arm non-randomized trial (DNDi-FEX-07-HAT) conducted in 45 adult and paediatric (aged ≥ 6 years and weighing ≥ 20 kg) patients with stage 2 ($n = 35$) and stage 1 ($n = 10$) r-HAT in Malawi and Uganda. The primary objective of the study was to demonstrate that the fatality rate at end of hospitalization was lower than a predetermined unacceptable fatality rate of 8.5%.

The primary endpoint was the fatality rate at end of hospitalization (day 12 to day 18), defined as the rate of fatalities possibly related to r HAT or to fexinidazole (according to the data safety monitoring board) in patients with stage 2 r-HAT. The population analysed for the primary endpoint was 34 stage-2 r-HAT patients who could be evaluated. One patient was excluded due to death on day 8 for a reason considered unrelated to r-HAT or treatment. The fatality rate at end of hospitalization was 0.0% (90% confidence interval (CI) 0.00% to 8.43%). Analyses in the modified intention-to-treat population ($n = 35$) and the total population ($n = 44$) reported fatality rates of 0.00% (90% CI 0.00% to 8.20%) and 0.0% (90% CI 0.00% to 6.58%), respectively. As the upper limit of the 90% CI was less than 8.5%, thereby excluding the threshold of unacceptable fatality rate, the null hypothesis was rejected.

Secondary efficacy endpoints were related to failure rates in r-HAT patients who could be evaluated and were assessed at end of hospitalization and at 12 months (end of study) in stage 2, stage 1 and the total evaluable population. Failure was assessed by the presence of trypanosomes in blood or cerebrospinal fluid at the end of treatment, death related to r-HAT or study treatment at end of hospitalization, or absence of clinical improvement leading to the use of rescue medication. Predetermined unacceptable failure rates were 9% at the end of hospitalization and 12% at 12 months. At the end of hospitalization, the failure rate in the evaluable stage 2 r-HAT patients was 0.0% (90% CI 0.00% to 8.43%). Results in the total evaluable population were similar. The sample size of stage 1 r-HAT patients ($n = 10$) was too small to be compared to the unacceptable failure rate. At 12 months, the failure rate in the stage 2 r-HAT patients who could be evaluated was 2.94% (90% CI 0.15% to 13.21%). In the overall population, the failure rate was 2.27% (90% CI 0.12% to 10.34%). No failures were reported in evaluable patients with stage 1 r-HAT.

Summary of evidence: harms

No new safety signals were reported for r-HAT patients and safety findings were generally consistent with the safety profile of fexinidazole established from previous studies in healthy subjects and patients with g-HAT.

A total of 45 patients with r-HAT were exposed to fexinidazole in the above-mentioned trial. During hospitalization, 40 treatment-emergent adverse events were reported in 22/45 (49%) r HAT patients. Seven treatment-emergent

adverse events were reported in five patients and were considered to be mild-to-moderate intensity and not serious. These events included electrocardiogram U-wave abnormalities, QT prolongation (QTcF < 500 ms), increased blood pressure, gastritis and vomiting. A total of 32 non-serious adverse events considered unrelated to treatment occurred in 18 patients. One serious adverse event of acute renal injury was reported in one patient. It was considered unrelated to the treatment or the disease, led to permanent treatment discontinuation after seven doses and to the patient's death on day 8.

During the follow-up period (starting from the month-1 visit), only adverse events considered possibly related to fexinidazole and all serious adverse events were reported. Two serious adverse events considered unrelated to the treatment (or disease) were reported in two patients. Overall, no adverse events of special interest, defined as neuropsychiatric signs and symptoms (excluding headaches and insomnia) requiring specialized therapeutic intervention, were reported.

Additional evidence

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WHO guidelines

The 2024 WHO guidelines for the treatment of HAT (*10*) include the following conditional recommendations for the use of fexinidazole in the treatment of r-HAT.

- In patients aged ≥ 6 years and with body weight ≥ 20 kg with first-stage r-HAT, use fexinidazole over suramin (very low-certainty evidence)
- In patients aged ≥ 6 years and with body weight ≥ 20 kg with second-stage r-HAT, use fexinidazole over melarsoprol (very-low-certainty evidence). Melarsoprol may be preferred in patients who: are unable to swallow; have a contraindication to fexinidazole; have persistent vomiting; or have questionable oral absorption.
- In pregnant women, given the rapid clinical evolution of r-HAT, treatment cannot usually be delayed. Clearly explain the benefits and risks to the patient and their relatives. Fexinidazole and pentamidine are preferred. Suramin and melarsoprol may become necessary as rescue treatment (very-low-certainty evidence).
- For fexinidazole to be absorbed at therapeutic levels, it must be taken in a fed condition (i.e. with or after food). As a condition of prescribing, the prescriber must have confidence in the availability of food for the patient, which will be eaten immediately before administration of the medicine each day (low-certainty evidence).
- Each intake of fexinidazole must be supervised by a trained health staff who must ensure that the patient is in a fed condition (directly observed treatment) (very-low-certainty evidence).

- Hospitalization is preferred and should be mandatory in patients presenting with psychiatric disorders, a history of alcohol use disorder, body weight lower than 35 kg, and vomiting following fexinidazole administration (very-low-certainty evidence).

Costs/cost–effectiveness

Medicines for treatment of HAT are provided free of charge to WHO through a public–private partnership between WHO/Sanofi (eflornithine, fexinidazole, melarsoprol and pentamidine) and WHO/Bayer AG (nifurtimox and suramin).

Sanofi signed an agreement with WHO in 2001, under which medicines for HAT are donated to WHO, to be used exclusively for its treatment. Requests for supplies are made to WHO by governments of disease-endemic countries and organizations working in association with these governments. Stock management and shipment of the medicines are undertaken by Médecins sans Frontières-Logistique according to the singed agreement. Transport costs are paid by Sanofi.

In the same way as is currently done for fexinidazole for g-HAT, fexinidazole will be distributed free of charge in countries endemic for r-HAT through the WHO Department of Control of Neglected Tropical Diseases to national sleeping sickness control programmes and from there to the treatment centres. The product will not be available through pharmacies or out of the predefined distribution system. No return on investment is expected.

Availability

Fexinidazole is currently approved in three countries worldwide: Democratic Republic of the Congo, Uganda and the United States of America.

On 14 December 2023, Sanofi received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use on the extension of indications for fexinidazole to include treatment of both first- and second-stage r-HAT. The extension of indications has also been approved in the Democratic Republic of the Congo and a registration application was submitted in May 2024 in Uganda.

Specific regulatory and distribution procedures for HAT therapies are in place. The current HAT medicines are not registered in all endemic countries but are registered in at least one Stringent Regulatory Authority. The stand-alone distribution system for all HAT medicines including fexinidazole is managed by WHO. The system allows import and distribution in other endemic countries through a letter of interest from national authorities to WHO, stating the inclusion of fexinidazole in the national HAT treatment policy.

The same distribution system will apply to fexinidazole for r-HAT in the corresponding endemic countries.

Other considerations

HAT is categorized as first-stage or second-stage for the purpose of guiding therapeutic choices via cerebrospinal fluid examination:

- first-stage (haemo-lymphatic stage): ≤ 5 white blood cells/μL AND no trypanosomes in cerebrospinal fluid
- second-stage (meningo-encephalitic stage): > 5 white blood cells/μL OR trypanosomes in cerebrospinal fluid.

Because fexinidazole is effective for both stages of HAT, cerebrospinal fluid examination is needed only to guide the choice of treatment for patients who are not captured by the approved indications for fexinidazole (i.e. aged < 6 years or body weight < 20 kg, or who have contraindications to the use of the medicines). Diagnostic tests for basic cerebrospinal fluid profile are included on the WHO Model List of Essential In Vitro Diagnostics (*11*).

Committee recommendations

The Expert Committee acknowledged the public health relevance of human African trypanosomiasis due to *Trypanosoma brucei rhodesiense* as a rare, but serious neglected tropical disease, that is usually fatal if untreated.

The Committee noted the evidence for fexinidazole comes from a single trial in a small number of patients, which demonstrated the effectiveness of the medicine in reducing fatality rates to within acceptable limits, albeit with limited follow-up. The Committee also noted that no new safety signals beyond those already known for fexinidazole were identified.

The Committee acknowledged support for the inclusion of fexinidazole on the EML and EMLc from the WHO technical department and that fexinidazole is recommended in current WHO guidelines for the treatment of African trypanosomiasis due to *T. b. rhodesiense* infection.

The Committee considered that as an orally administered treatment, the use of fexinidazole may offer both patient and health-system advantages compared with parenteral administration of other medicines used in the treatment African trypanosomiasis due to *T. b. rhodesiense* (e.g. suramin sodium, melarsoprol).

The Committee also noted that fexinidazole would be provided free of charge through the WHO Department of Control of Neglected Tropical Diseases to national sleeping sickness control programmes and treatment centres.

Based on these considerations, the Expert Committee therefore recommended the inclusion of fexinidazole on the EML and EMLc for the new indication of treatment of first- and second-stage African trypanosomiasis due to *T. b. rhodesiense* infection.

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Section 7: Medicines for cystic fibrosis

Elexacaftor + tezacaftor + ivacaftor – addition – EML and EMLc

Elexacaftor + tezacaftor + ivacaftor	**ATC code: R07AX32**
Ivacaftor	**ATC code: R07AX02**

Proposal

Addition of elexacaftor + tezacaftor + ivacaftor fixed-dose combination, and single-agent ivacaftor to the core list of the EML and EMLc for treatment of people with cystic fibrosis aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive to treatment based on in vitro data.

Applicant

Dr Andrew Hill, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, United Kingdom of Great Britain and Northern Ireland; Right to Breathe campaign for equitable global access to CFTR modulators

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

7 Medicines for cystic fibrosis

Dose form(s) & strengths(s)

Elexacaftor + tezacaftor + ivacaftor

Granules: 80 mg + 40 mg + 60 mg, 100 mg + 50 mg + 75 mg in sachet
Tablet: 50 mg + 25 mg + 37.5 mg, 100 mg + 50 mg + 75 mg

Ivacaftor

Granules: 59.5 mg, 75 mg in sachet
Tablet: 75 mg, 150 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Elexacaftor + tezacaftor + ivacaftor and ivacaftor have not previously been evaluated for inclusion on the Model Lists. Currently no medications to treat the underlying cause of cystic fibrosis are listed on the EML or EMLc.

Pancreatic enzymes, a supportive therapy with a role in alleviating some gastrointestinal features of cystic fibrosis, are listed on the complementary list of the EMLc.

Public health relevance

Cystic fibrosis is a life-shortening genetic disease that follows an autosomal recessive inheritance pattern (*1*). It is caused by mutations in the *CFTR* gene. The *CFTR* protein, encoded by this gene, functions as a cyclic adenosine monophosphate (cAMP)-activated chloride channel (*2*), playing a critical role in regulating the osmotic balance and viscosity of mucus (*3*). F508del, a more severe variant, is the most common *CFTR* variant worldwide (*4*). The lungs of individuals with cystic fibrosis are normal in utero, at birth and throughout the immediate postnatal period. Over time, recurrent airway infections and the resultant inflammatory processes give rise to cumulative respiratory disease and structural damage. Eventually, this progressive deterioration leads to airway obstruction and failure to ventilate the lungs. Pulmonary disease is the leading cause of death in people with cystic fibrosis (*2*).

Research published in 2024 estimated that there were 188 336 individuals with cystic fibrosis in 96 countries globally. Among this population, it was estimated that 111 767 (59%) had been diagnosed and 51 322 (27%) were receiving treatment with elexacaftor + tezacaftor + ivacaftor. Almost 15 000 of people diagnosed are living in countries where this medicine is not accessible. Of people thought to be undiagnosed, 82% live in low- and middle-income countries (*5*).

People with cystic fibrosis experience educational disadvantages as a result of the cumulative effect of disease symptoms, complex treatment regimens and hospital attendance (*6*). The physical manifestations of the disease may also limit an individual's capacity to maintain employment (*7*). As such, people with cystic fibrosis are less likely to be employed compared with the general population, and many face substantial financial disadvantage. Additionally, parents, spouses and carers of people with cystic fibrosis are psychologically affected (*8*), are less likely to be in full-time employment and experience financial hardship (*9*).

Summary of evidence: benefits

The applicants performed a systematic literature search for studies reporting efficacy and/or tolerability of elexacaftor + tezacaftor + ivacaftor, identifying seven systematic reviews (*10*–*16*) and seven randomized trials (*17*–*23*). Most trials (5/7, 71%) involved patients with cystic fibrosis aged ≥ 12 years. Only one trial assessed efficacy and safety in patients with cystic fibrosis without F508del mutations. Because no single systematic review synthesized the evidence from all available randomized trials, the applicants extracted data on efficacy outcomes from the seven trials and performed their own meta-analysis, and risk of bias and GRADE assessment. The included trials were all conducted in high-income countries. The application stated that these studies represented populations of different ages and sexes and could be reasonably extrapolated to people with cystic fibrosis in low- and middle-income countries.

The efficacy outcomes of interest included absolute percentage change in predicted force expiratory volume in one second ($ppFEV_1$) and sweat chloride concentration. These outcomes were chosen because they have been shown to be strong predictors of survival in people with cystic fibrosis. The findings of the meta-analysis are summarized below.

People with cystic fibrosis aged ≥ 12 years with F508del mutations

There was high-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than both placebo (mean difference (MD) 14.24, 95% confidence interval (CI) 12.79 to 15.68; two randomized controlled trials, 436 participants) and dual *CFTR* modulator therapy (MD 10.15, 95% CI 10.15 to 11.65; three randomized controlled trials, 330 participants) at improving $ppFEV_1$ in patients whose *CFTR* genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation.

There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than dual *CFTR* modulator therapy (MD 3.50, 95% CI 2.24 to 4.76; one randomized controlled trial, 258 participants) at improving $ppFEV_1$ in patients whose *CFTR* genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation.

There was high-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than both placebo (MD −41.43, 95% CI −43.86 to −38.99; two randomized controlled trials, 436 participants) and dual *CFTR* modulator therapy (MD −43.37, 95% CI −46.08 to −40.66; three randomized controlled trials, 330 participants) at lowering sweat chloride concentration in patients whose *CTFR* genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation.

There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than dual *CFTR* modulator therapy (MD −23.00, 95% CI −25.98 to −20.02; one randomized controlled trial, 258 participants) at lowering sweat chloride concentration in patients whose *CFTR* genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation.

People with cystic fibrosis aged < 12 years with F508del mutations

There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than placebo at both improving $ppFEV_1$ (MD 11.00, 95% CI 1.81 to 20.19; one randomized controlled trial, 121 participants) and lowering sweat chloride concentration (MD −51.20, 95% CI −55.22 to −47.18; one randomized controlled trial, 121 participants) in patients whose *CFTR* genotype was heterozygous for F508del mutation and minimal function mutation.

People with cystic fibrosis aged > 6 years without F508del mutations

There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was more effective than placebo at improving ppFEV1 (MD 9.38, 95% CI 7.43 to 11.32; one randomized controlled trial, 307 participants) and lowering sweat chloride concentration (MD −28.30, 95% CI −32.06 to −25.54; one randomized controlled trial, 307 participants).

Summary of evidence: harms

The findings of the meta-analysis performed by the applicants are summarized below.

People with cystic fibrosis aged ≥ 12 years with F508del mutations

There was high-certainty evidence of no significant differences in the rate of total adverse events between elexacaftor + tezacaftor + ivacaftor and placebo (odds ratio (OR) 1.16, 95% CI 0.55 to 2.44; two randomized controlled trials, 436 participants) and dual *CFTR* modulator therapy (OR 1.20, 95% CI 0.70 to 2.05; three randomized controlled trials, 330 participants) in patients whose *CTFR* genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation.

There was high-certainty evidence of no significant difference in the rate of serious adverse events with elexacaftor + tezacaftor + ivacaftor compared with placebo (OR 0.60, 95% CI 0.36 to 1.01; two randomized controlled trials, 436 participants) or dual *CFTR* modulator therapy (OR 0.66, 95% CI 0.30 to 1.46; three randomized controlled trials, 330 participants) in patients whose *CTFR* genotypes were homozygous for F508del mutation or heterozygous for F508del mutation and minimal function mutation.

There was moderate-certainty evidence of no significant difference between elexacaftor + tezacaftor + ivacaftor and dual *CFTR* modulator therapy in the rate of total adverse events (OR 1.04, 95% CI 0.62 to 1.74; one randomized controlled trial, 258 participants) and serious adverse events (OR 0.41, 95% CI 0.14 to 1.22; one randomized controlled trial, 258 participants) in patients whose *CTFR* genotypes were heterozygous for F508del mutation and Gating mutation or heterozygous for F508del mutation and residual function mutation.

People with cystic fibrosis aged < 12 years with F508del mutations

There was moderate-certainty evidence that elexacaftor + tezacaftor + ivacaftor was associated with a significantly reduced risk of total adverse events compared with placebo (OR 0.28, 95% CI 0.08 to 0.93; one randomized controlled trial, 121 participants). There was moderate-certainty evidence of no significant difference between elexacaftor + tezacaftor + ivacaftor and placebo for serious adverse events (OR 0.41, 95% CI 0.12 to 1.42; one randomized controlled trial, 121 participants) in patients whose *CFTR* genotype was heterozygous for F508del mutation and minimal function mutation.

People with cystic fibrosis aged > 6 years without F508del mutations

There was moderate-certainty evidence of no significant differences between elexacaftor + tezacaftor + ivacaftor and placebo for total adverse events (OR 1.66, 95% CI 0.69 to 3.97; one randomized controlled trial, 307 participants) or serious adverse events (OR 0.59, 95% CI 0.28 to 1.22; one randomized controlled trial, 307 participants).

Other evidence for safety

A 2023 systematic review and single-arm meta-analysis of 53 studies (11 randomized controlled trials, 42 observational studies) included an evaluation of the prevalence of adverse events in patients with cystic fibrosis (2 to 72 years) receiving elexacaftor + tezacaftor + ivacaftor (*11*). The overall rate of adverse events associated with treatment was 82.4%, with most being associated with disease development and of mild to moderate severity. The rate of severe adverse events was 6.6%. The most frequently reported adverse events were cough (23.8%), rhinorrhoea (21.2%) and headache (16.1%). Infective pulmonary exacerbations of cystic fibrosis were reported in 14.8% of patients.

The safety profile of elexacaftor + tezacaftor + ivacaftor in children younger than 12 years has been reported in phase III trials and appears to be consistent with that observed in older patients (*24*–*26*) .

Observational studies have reported neuropsychiatric adverse events including anxiety, so-called brain fog, depression and sleep disturbances, in

adults and children receiving elexacaftor + tezacaftor + ivacaftor (27–29). In an open-label phase III trial of elexacaftor + tezacaftor + ivacaftor in children aged 2–5 years, one participant discontinued treatment due to abnormal behaviour, suspected to be treatment-related (26). In an open-label phase III extension trial in children aged 6–11 years, one participant discontinued treatment due to moderate severity aggression, thought to be unrelated to treatment (25). In both cases, there was resolution after treatment discontinuation. In a post-marketing study of preschool-aged children started on elexacaftor + tezacaftor + ivacaftor, 93/197 (47%) children were observed to have sudden abnormal behavioural changes as reported by parents that were suspected to be treatment-related. Four children discontinued treatment (30). A 2024 review of depression-related adverse events after starting elexacaftor + tezacaftor + ivacaftor analysed safety data from clinical trials, post-marketing safety reports, registry-based post-authorization safety studies and published literature. The review found that depression symptoms and depression-related events reported in patients treated with elexacaftor + tezacaftor + ivacaftor were generally consistent with background epidemiology of these events in patients with cystic fibrosis and did not suggest a causal relationship with elexacaftor + tezacaftor + ivacaftor treatment (31).

Cystic fibrosis clinics have implemented off-label dose-reduction strategies with elexacaftor + tezacaftor + ivacaftor in individuals experiencing neuropsychiatric adverse events. Case series and case reports have observed resolution of adverse events after dose reduction while still maintaining the efficacy of the treatment (27, 28).

Additional evidence

Modulator-sparing regimens

Exposures of elexacaftor, tezacaftor, and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors (e.g., clarithromycin, ritonavir), and product labels recommend dose adjustment when strong or moderate CYP3A inhibitors are used concomitantly with elexacaftor + tezacaftor + ivacaftor. For example, with concomitant use of strong CYP3A inhibitors, the recommended dosing frequency of elexacaftor + tezacaftor + ivacaftor is twice weekly (instead of daily). Dosing strategies taking advantage of the pharmacokinetic enhancement of *CFTR* modulators by strong CYP3A inhibitors have been used to reduce the cost of treatment in some settings, without loss of clinical effectiveness (32, 33).

WHO guidelines

WHO guidelines for the treatment of cystic fibrosis are not currently available.

Costs/cost–effectiveness

The application included an assessment of the cost–effectiveness of elexacaftor + tezacaftor + ivacaftor from health technology assessments from nine countries where the medicine is available. List prices, cost–effectiveness decisions and reimbursement arrangements (e.g. price reductions and confidential pricing agreements) were summarized. List prices were between 100 000 United States dollars (US$) and US$ 300 000 per person per year in all countries evaluated except for South Africa, where legal challenges have resulted in a substantially lower price. When South Africa was excluded, the average list price was US$ 237 193, well above usual cost–effectiveness thresholds. Health technology assessments found that the medicine price had the greatest effect on cost–effectiveness and often advocated for price reductions of about 70– 90% in order for elexacaftor + tezacaftor + ivacaftor to be considered cost-effective.

A 2022 study estimated the minimum costs of production of *CFTR* modulators, including elexacaftor + tezacaftor + ivacaftor, in comparison with current list prices in the United States (*34*). The study estimated the cost of production to be US$ 5676 per patient per year, with an annual treatment cost of US$ 489 million for all eligible diagnosed cystic fibrosis patients globally. In contrast, the estimated annual treatment cost using the United States list price was US$ 31.2 billion.

The application highlighted dose-reduction strategies that have been investigated and have the potential to reduce the cost of treatment with elexacaftor + tezacaftor + ivacaftor, without loss of efficacy, including co-administration with strong CYP3A inhibitors and other dose reductions (*33*, *35*, *36*). However, currently, the evidence for dose reduction is limited.

Availability

Elexacaftor + tezacaftor + ivacaftor, and single-agent ivacaftor are currently approved in only a limited number of (mainly high-income) countries.

Elexacaftor + tezacaftor + ivacaftor is under patent until 2037, while patents for single-agent ivacaftor are reported to expire between 2025 and 2027.

Other considerations

Elexacaftor + tezacaftor + ivacaftor is subject to additional monitoring by the Australian Therapeutic Goods Administration, European Medicines Agency and United Kingdom Medicines and Healthcare Products Regulatory Agency under the black triangle scheme (indicated by a black inverted triangle (▼)) in the product information.

Committee recommendations

The Expert Committee recognized the significant public health relevance of effective treatments for cystic fibrosis. The Committee noted that no medicines currently listed on the EML or EMLc treat the underlying cause of cystic fibrosis. Pancreatic enzymes, which provide supportive care for gastrointestinal symptoms, are listed on the complementary list of the EMLc. The addition of elexacaftor + tezacaftor + ivacaftor would represent the first disease-modifying therapy for cystic fibrosis on the Model Lists.

The Committee reviewed evidence from seven randomized controlled trials and multiple systematic reviews. The combination therapy demonstrated clinically meaningful improvements in lung function ($ppFEV_1$) and sweat chloride concentration across age groups and genotypes, particularly in individuals with at least one F508del mutation. These outcomes are considered strong predictors of long-term survival and reduced disease progression. The safety profile was generally favourable, with most adverse events being mild to moderate. However, the Committee noted reports of neuropsychiatric adverse events, including anxiety and sleep disturbances, which may require dose adjustment or discontinuation. These events appear to be reversible and emerging clinical practice includes dose-reduction strategies to manage them.

The Committee acknowledged that the current list prices of elexacaftor + tezacaftor + ivacaftor are well above conventional cost–effectiveness thresholds. However, the Committee also noted that the estimated minimum cost of production is substantially lower. Opportunities for lower dosing (without loss of clinical benefit) to reduce cost, including pharmacokinetic enhancement strategies and half-dose regimens, were highlighted as promising but require further validation as supporting evidence is currently limited. The Committee emphasized the importance of pursuing mechanisms to improve affordability, including generic competition and pooled procurement.

The Committee noted that the medicine is currently approved in a limited number of high-income countries, and it remains under patent until 2037. Access in low- and middle-income countries is extremely limited. The Committee considered that inclusion on the EML and EMLc could support efforts to expand regulatory approval, stimulate development of generics and promote equitable access. While agreeing that compulsory licensing should be reserved for appropriate circumstances, the Committee considered this case as one where such mechanisms could have a substantial impact on pricing and access. Although granting a compulsory license for elexacaftor + tezacaftor + ivacaftor may be challenging in practice, the Committee acknowledged the role of countries' compulsory license requests as a negotiation tool to accelerate procedures and stimulate generic development.

WHO guidelines for the treatment of cystic fibrosis are not currently available. The Committee considered that inclusion of this medicine on the Model Lists could inform future guideline development and support comprehensive care strategies for cystic fibrosis.

Based on these considerations, the Expert Committee recommended the addition of elexacaftor + tezacaftor + ivacaftor to the core list of the EML and EMLc for the treatment of cystic fibrosis in individuals aged 2 years and older with at least one F508del mutation or another responsive *CFTR* mutation. The Committee acknowledged the high cost and limited availability of the medicine but considered that its inclusion on the Model Lists could catalyse actions to improve access and affordability. The Committee also emphasized the importance of close monitoring for neuropsychiatric adverse events and encouraged further research into dose optimization strategies to reduce treatment costs.

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Section 8: Immunomodulators and antineoplastics

8.2 Antineoplastics and supportive medicines

8.2.1 Cytotoxic medicines

Temozolomide – addition – EML and EMLc

Temozolomide **ATC code: L01AX03**

Proposal

Addition of temozolomide to the complementary list of the EML and EMLc for treatment of:

- newly diagnosed high-grade glioma in patients older than 3 years, in combination with radiotherapy;
- relapsed or refractory high-risk neuroblastoma, in combination with irinotecan or topotecan,;
- relapsed Ewing sarcoma, in combination with irinotecan;
- other resistant or relapsed paediatric solid tumours in palliative settings as monotherapy.

Applicant

European Society for Paediatric Oncology Essential Medicines team

WHO technical department

The technical team in cancer in the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed the application. The team commented that evidence supporting the efficacy of temozolomide as a single agent in proposed relapsed paediatric cancers was limited and that for newly diagnosed high-grade gliomas, inconsistencies in outcomes in different studies have been reported. Additionally, in heavily treated patients with refractory or relapsed solid tumours, treatment is associated with haematological toxicity requiring continuous laboratory monitoring of white blood cells which may not be feasible in resource-constrained settings. The technical team did not support the inclusion of temozolomide on the Model Lists at this time, suggesting that a decision could be deferred until more mature data become available.

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strengths(s)

Temozolomide

Capsule: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg
Powder for injection: 100 mg in vial

Irinotecan

Injection: 50 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial

Topotecan

Injection: 1 mg/mL (as hydrochloride) in 1 mL, 2 mL, 4 mL vial
Powder for injection: 1 mg, 4 mg (as hydrochloride) in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Medicines for the treatment of high-grade glioma and neuroblastoma have not previously been evaluated for inclusion in the Model Lists.

Medicines for the treatment of Ewing sarcoma were evaluated by the Expert Committee in 2015. Based on the evidence presented in the application, the Committee recommended the inclusion of cyclophosphamide, doxorubicin, etoposide, ifosfamide, mesna and vincristine on the complementary list of the EML and EMLc for the treatment of Ewing sarcoma (*1*). In 2021, the Expert Committee also recommended the inclusion of dactinomycin on the complementary list of the EML and EMLc for this indication (*2*).

Irinotecan is currently included on the Model Lists for other indications, that is, metastatic colorectal cancer, nephroblastoma and rhabdomyosarcoma.

Public health relevance

The application included data from the International Agency for Research on Cancer published in 2017 (*3*), which reported the following age-specific incidence rates among children 0 to 14 years for the indications being proposed for listing:

- central nervous system and miscellaneous intracranial and intraspinal neoplasms – from 3.4 per million in Uganda to 49.7 per million in Italy;
- neuroblastoma and ganglioneuroblastoma – from 0.4 per million in Cameroon to 21.5 per million in Italy;

- Ewing tumour and related sarcomas of bone – from 0.2 per million in Ecuador, Kuwait, and Uganda to 7.5 per million in New Zealand.

Data from the United States reported annual average number of cases in children 0 to 14 years was 32 and 78 for anaplastic astrocytoma and glioblastoma, respectively. The 5- and 10-year relative survival rates among children aged 0 to 14 years with anaplastic astrocytoma were 25.5% and 20.4%, respectively, and with glioblastoma were 20.7% and 17.1%, respectively. Median survival of 21 months and 9 months were reported for anaplastic astrocytoma and glioblastoma, respectively (4).

The application reported that survival data from low- and middle-income countries were not available.

Summary of evidence: benefits

High-grade glioma

The HIT-HGG 2007 trial was a multicentre, prospective phase II clinical trial that aimed to demonstrate therapeutic non-inferiority between temozolomide radiochemotherapy versus cisplatinum-based radiochemotherapy in paediatric patients aged 3 to 18 years with high-grade gliomas (5). Between 2009 and 2016, 438 participants were enrolled to receive temozolomide combined with craniospinal irradiation, and 438 participants from the HIT-GMB-C/-D trial of cisplatinum-based radiochemotherapy served as historical controls. The results for 6-months event-free survival and overall survival indicated that the primary objective of non-inferiority was achieved. Subgroup analyses showed longer event-free survival in temozolomide-treated patients with pontine (8.2 months versus 6.2 months; $P = 0.008$) and non-pontine tumours (10.7 months versus 7.4 months; $P < 0.0001$). Overall survival was improved in temozolomide-treated patients with non-pontine tumours (median overall survival 19.3 months versus 16.2 months; $P = 0.018$), but not in those with pontine tumours (median overall survival 11.4 months versus 11.3 months; $P = 0.402$).

The HIT-HGG 2013 trial is a multicentre, prospective, phase III trial that is investigating the effect of adding valproic acid to standard treatment with temozolomide radiochemotherapy in 198 paediatric patients aged 3 to 18 years with high-grade glioma (6). Results are not yet reported.

Neuroblastoma

A 2006 study described the antitumour effects of a 5-day course of irinotecan 50 mg/m^2 per day (intravenous) plus temozolomide 150 mg/m^2 per day (oral) every 3–4 weeks in 49 patients aged between 2 and 26 years with relapsed or refractory neuroblastoma (7). Nineteen patients were assessable for response of refractory disease. Of these, nine showed evidence of disease regression, including

two complete responses and seven objective responses. Of 17 patients treated for progressive disease, three showed evidence of disease regression, including one partial response and two objective responses.

A phase II study evaluated the response rate of irinotecan plus temozolomide in 55 children aged younger than 3 months to 18.5 years with relapsed or refractory neuroblastoma (*8*). Participants received irinotecan 10 mg/m^2 per dose (intravenous) 5 days a week for 2 weeks plus temozolomide 100 mg/m^2 per dose (oral) for 5 days every 3 weeks. Two strata of patients were defined, one that could be evaluated for response by cross-sectional imaging (stratum 1, $n = 28$) and the other that could be assessed by bone marrow aspirate/biopsy or metaiodobenzylguanidine scan only (stratum 2, $n = 27$). Participants who received at least two courses of treatment were considered suitable for evaluation of response. An objective response (complete response or partial response) was reported in 8/55 (14.5%) participants overall, 3/28 in stratum 1 (10.7%) and 5/27 (18.5%) in stratum 2. Stable disease was reported in 14/28 (50.0%) and 15/27 (55.5%) participants in stratums 1 and 2, respectively.

A phase II study evaluated the objective response rate following two cycles of temozolomide in combination with topotecan (TOTEM regimen) in 38 children aged between 6 months and ≤ 20 years with relapsed or refractory neuroblastoma (*9*). Participants received oral temozolomide 150 mg/m^2 followed by intravenous topotecan 0.75 mg/m^2 for 5 consecutive days every 28 days. The study endpoint was objective response rate defined as complete or partial response after two cycles of treatment. After two cycles, the estimated objective response rate was 18% (seven participants achieved a partial response, and no participants achieved a complete response). For the outcome of best response at any time of evaluation, the objective response rate was 24% (six participants achieved a partial response and three participants achieved a complete response). The estimated tumour control rate (combining complete, partial and mixed response and stable disease) was 79% (95% confidence interval (CI) 63% to 90%). With median follow-up of 28.5 months, median progression-free survival was 10.3 months (95% CI 6.4 to 17.8 months) and the 12-month progression-free survival rate was 45%. Median overall survival was 25.8 months (95% CI 11.3 to not estimated) and the 12-month overall survival rate was 58%.

The application also described further studies in which temozolomide-based chemotherapy was used in combination with other therapies, e.g. temsirolimus, anti-GD2 monoclonal antibodies and bevacizumab (*10*–*13*).

Ewing sarcoma

A retrospective study reviewed efficacy and toxicity outcomes of irinotecan and temozolomide in adult and paediatric patients with relapsed Ewing sarcoma from electronic medical records in two institutions in Australia and Jordan (*14*).

Records for 53 eligible patients were identified (16 paediatric and 37 adult), all of whom received temozolomide 100 mg/m^2/day on days 1 to 5 of each treatment cycle. Additionally, 29 patients received irinotecan < 250 mg/m^2/cycle and 24 patients received ≥ 250 mg/m^2/cycle. Of 43 patients assessable for response, 12 (28%) achieved an objective response (one complete response, 11 partial responses), 19 (44%) had disease progression and 12 (28%) had stable disease. No significant differences were noted between age cohorts in the overall response rate (36% versus 25% for paediatric patients and adults, respectively; $P = 0.47$). For progression-free survival, 52 patients were assessable. Median progression-free survival was 3.8 months and the 6-month progression-free survival rate was 39%. Median progression-free survival was significantly longer in paediatric patients than in adults (7.4 months versus 2.2 months; $P = 0.039$).

Another multicentre retrospective study analysed efficacy outcomes of irinotecan and temozolomide in adult ($n = 34$) and paediatric ($n = 17$) patients with recurrent Ewing sarcoma in Italy and the United Kingdom (*15*). Administered doses were temozolomide 100 mg/m^2/day and irinotecan 40 mg/m^2/day, on days 1–5 of each 21-day treatment cycle. An objective response was achieved by 17/51 (33%) patients (5 with complete response, 12 with partial response). No significant difference was seen in the objective response rate by age cohort. Median progression-free survival was 3.9 months and the 6-month progression-free survival rate was 49%, significantly influenced by Eastern Cooperative Oncology Group (ECOG) performance status and lactate dehydrogenase levels. The 1-year overall survival rate was 55%, with response to treatment and ECOG score being independent predictors of outcome.

Another retrospective study evaluated the use of irinotecan and temozolomide in 20 patients with recurrent or progressive Ewing sarcoma at Memorial Sloan-Kettering Cancer Center in the United States of America (*16*). Of the 19 patients who could be evaluated, the objective response rate was 63% (five complete responses and seven partial responses). Progressive disease was reported in seven patients. After a median follow-up of 25.7 months, the median time to progression was 8.3 months overall and 16.2 months for patients with recurrent disease. Time to progression was better in patients with a sustained 2-year first remission and those with localized, rather than metastatic, disease.

Other resistant or relapsed solid tumours

An off-label, compassionate-use study in Italy evaluated the therapeutic activity and toxicity of temozolomide in 52 children with relapsed solid tumours 17 with neuroblastoma, eight with medulloblastoma, eight with brain stem glioma, six with neuroectodermal tumours, four with Ewing sarcoma, three with anaplastic astrocytoma, two with rhabdomyosarcoma, two with ependymoma, one with hepatocarcinoma and one with osteosarcoma (*17*). Temozolomide was

administered at a dose of 180 mg/m²/day or 215 mg/m²/day 5 days, repeated every 21–28 days, in patients with prior craniospinal irradiation or who had relapsed after bone marrow transplantation and in patients without prior craniospinal irradiation, respectively. Twenty-seven patients were eligible for response evaluation after two courses. The objective response rate was 13.4% (one complete response, two partial responses and four minor responses). Stable disease was reported in 38.4% of patients, and 48.1% of patients had progressive disease. Median survival was 7.8 months and time to progression was 3.4 months.

A multicentre retrospective review study investigated response rate and progression-free survival with temozolomide in combination with irinotecan and vincristine in the treatment of 19 patients aged 2–17 years with relapsed rhabdomyosarcoma (*18*). Administered doses were vincristine 1.5 mg/m² intravenous on day 1, irinotecan 50 mg/m² intravenous or 70–100 mg/m² orally on days 1–5, and temozolomide 100–150 mg/m² orally on days 1–5 every 21 days. Fifteen patients were evaluable for response. Four patients achieved stable disease, and 11 patients had progressive disease. No complete or partial responses were reported. The objective response rate was 26.7%. Progression-free survival at 3 months was 23%. Toxicity data were not collected.

Summary of evidence: harms

In the HIT-HGG 2007 trial, the toxicity profile of temozolomide radiochemotherapy was considered favourable, with less toxicity observed in comparison with cisplatinum- or methotrexate-based radiochemotherapy protocols for high-grade glioma (*5*). Most adverse events ≥ grade 3 were haematological toxicity, hepatotoxicity and neurotoxicity.

In the phase II study of temozolomide plus irinotecan in the treatment of relapsed or refractory neuroblastoma, grade 3 or 4 adverse events included haematological toxicity (neutropenia, thrombocytopenia and anaemia) reported in almost 50% of patients. Less than 10% of patients developed evidence of infection while neutropenic. Grades 3 or 4 fever and infection were reported in about 20% of all patients, while grade 3 or 4 diarrhoea were reported in about 5% of all patients (*8*).

In the phase II study of temozolomide plus topotecan in the treatment of relapsed or refractory neuroblastoma, the most commonly reported adverse events were haematological toxicities, including grade 3 or 4 neutropenia and thrombocytopenia. Less than 10% of patients experienced febrile neutropenia (*9*).

In studies of temozolomide plus irinotecan in the treatment of Ewing sarcoma, toxicities were similar to those seen in studies for neuroblastoma (*14*–*16*).

In studies of temozolomide in other resistant or relapsed solid tumours, the most frequently reported toxicities were neutropenia and thrombocytopenia. Non-haematological adverse events were infrequent (*17*, *19*).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of high-grade glioma, neuroblastoma, or Ewing sarcoma are not currently available.

Costs/cost–effectiveness

No information on cost–effectiveness was presented in the application. The application presented limited information on the cost of temozolomide, irinotecan and topotecan in different settings.

Availability

Approved indications for temozolomide vary depending on jurisdiction. For example, in Europe, temozolomide has regulatory approval for use in children from the age of 3 years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. In the United States, temozolomide is approved only for use in adults.

Temozolomide is used off-label for the treatment of neuroblastoma, Ewing sarcoma and other paediatric solid tumours. Irinotecan and topotecan are used off-label for the indications proposed in the application.

Temozolomide, irinotecan and topotecan are widely available as innovator and generic brands.

Other considerations

As part of the WHO paediatric drug optimization exercise for cancer medicines, temozolomide was included as one of six paediatric cancer medicines prioritized for development of an age-appropriate formulation for children. The exercise noted that paediatric dosages of temozolomide are typically achievable with the available range of capsule sizes without imposing a significant pill burden. However, it was noted that use could be limited by the inability of some children to swallow capsules whole. The recommendation of the paediatric drug optimization exercise was to investigate and develop a more age-appropriate formulation in a non-liquid oral dosage form, predominantly for use in the treatment of relapsed or refractory disease (*20*).

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of temozolomide on the EMLc for the proposed indications. It highlighted that overall survival data were only available from two studies in high-grade glioma,

and thus the data are limited. Furthermore, the group judged that the benefits associated with oral administration of temozolomide in terms of feasibility and equity, including patient compliance and quality of life, would be likely to be offset by the increased risk of severe haematological toxicity and the need for monitoring of adverse events in the hospital.

Committee recommendations

The Expert Committee recognized the public health relevance of effective treatments for childhood cancers and acknowledged the goal of the WHO global initiative for childhood cancer to increase the survival rate of children with cancer globally to at least 60% by 2030, while reducing their suffering and improving their quality of life.

The Committee noted that temozolomide was identified as a priority paediatric cancer medicine during the WHO paediatric drug optimization exercise for cancer medicines for which development of a more age-appropriate oral formulation than currently available capsules was recommended.

For high-grade glioma, the Committee noted limited evidence of an overall survival benefit associated with temozolomide radiochemotherapy compared with cisplatinum-based radiochemotherapy in patients with non-pontine tumours. However, the magnitude of the survival gain was below the EML threshold of 4–6 months. In neuroblastoma, the Committee noted evidence from phase II studies that objective response rates for temozolomide plus irinotecan, and temozolomide plus topotecan were below 20%. In Ewing sarcoma, data from retrospective studies showed modest benefit for temozolomide plus irinotecan in objective response rates. Temozolomide has not been demonstrated to improve survival in patients with neuroblastoma or Ewing sarcoma.

In other refractory solid tumour types, the evidence of benefit was even more limited.

In terms of safety, the Committee noted that the main concerns with temozolomide were haematological toxicities, which can be severe and require inpatient monitoring and management.

Overall, the Committee considered that the balance of benefits to harm for temozolomide was not favourable.

Based on these considerations, the Expert Committee did not recommend the inclusion of temozolomide on the EML and EMLc for the treatment of high-grade glioma (as monotherapy), relapsed or refractory high-risk neuroblastoma (in combination with irinotecan or topotecan), relapsed Ewing sarcoma (in combination with irinotecan), or as monotherapy for treatment of other relapsed or refractory paediatric solid tumours as palliative treatment.

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8.2.2 Targeted therapies

Panitumumab – addition – EML

Panitumumab	ATC code: L01FE02

Proposal

Addition of panitumumab to the complementary list of the EML for treatment of adults with KRAS/NRAS wild-type metastatic colorectal cancer, in first-, second- and later lines of therapy.

Applicant

Resonance, Inc. Memphis, TN, United States of America

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed the application and advised that it did not support the inclusion of panitumumab on the EML because the therapeutic benefit was insufficient based on the available evidence.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Concentrate for solution for infusion: 20 mg/mL in 5 mL, 20 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Panitumumab has not previously been considered for inclusion on the EML for treatment of KRAS/NRAS wild-type metastatic colorectal cancer or any other indication.

The EML currently includes calcium folinate, capecitabine, fluorouracil, irinotecan and oxaliplatin for use in the treatment of metastatic colorectal cancer,

as part of the fluorouracil, leucovorin and oxaliplatin (FOLFOX), fluorouracil, leucovorin and irinotecan (FOLFIRI), or capecitabine and oxaliplatin (CapeOx) treatment regimens.

Panitumumab is indicated for treatment of adult patients with KRAS/NRAS wild-type metastatic colorectal cancer: in the first-line setting in combination with FOLFOX or FOLFIRI; in the second-line setting in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan); and as monotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

Public health relevance

Metastatic colorectal cancer is an advanced stage of disease in which tumour cells have migrated through either the bloodstream or lymphatic system to other organs such as the liver or lung. Around 20–25% of patients have metastatic disease at diagnosis and metastases eventually develop in up to 50% of all patients, most of whom die as a result (*1*–*3*). The 5-year relative survival rate is 5–15% in patients with widespread metastatic disease (*4*). The goals of therapy in metastatic colorectal cancer are to extend survival, potentially cure selected patients, prevent disease progression, reduce tumour-related symptoms and maintain health-related quality of life (*5*). The management of metastatic colorectal cancer involves numerous lines of systemic therapy (including chemotherapy and targeted biological agents), salvage surgery and maintenance therapy, interspersed with treatment-free intervals (*6*).

Globally in 2022, there were about 1.9 million new cases and more than 900 000 deaths from colorectal cancer. About 60% of incident cases and 70% of deaths occurred in low- and middle-income countries (*7*).

The primary target population for panitumumab is adult patients with KRAS/NRAS wild type metastatic colorectal cancer, which is responsible for most of the mortality in this disease, and which comprises about 50% of all metastatic colorectal cancer patients. Metastatic disease disproportionately affects patients in low- and middle-income countries due to delayed or intermittent screening programmes for colorectal cancer and other barriers to early diagnosis. The need for *KRAS/NRAS* testing to identify patients most likely to respond to treatment with panitumumab can also pose a barrier in low- and middle-income countries, where diagnostic capabilities are not available or affordable. However, the application reported that relevant diagnostic capabilities were increasingly available, especially in urban centres, academic centres or specialist cancer treatment facilities, which is anticipated to increase as further medicines-diagnostic combinations are made available.

Summary of evidence: benefits

Comparison of panitumumab and chemotherapy or best supportive care

A 2017 Cochrane systematic review and meta-analysis of 33 randomized controlled trials (15 025 participants) evaluated the efficacy and safety of epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer (*8*). Comparisons evaluated included: (i) EGFR monoclonal antibodies (cetuximab and panitumumab) plus standard therapy (chemotherapy or best supportive care) versus standard therapy alone; (ii) EGFR tyrosine kinase inhibitors plus standard therapy versus standard therapy alone; (iii) EGFR inhibitor plus standard therapy versus another EGFR inhibitor; and (iv) EGFR inhibitor, anti-angiogenic therapy plus standard therapy versus anti-angiogenic therapy plus standard therapy alone.

For the comparison of EGFR monoclonal antibody added to standard therapy in patients with KRAS exon 2 wild-type metastatic colorectal cancer, pooled analysis of trials in first-, second- and third-line treatment settings showed high quality evidence that EGFR monoclonal antibody therapy added to standard therapy improved progression-free survival (hazard ration (HR) 0.70, 95% confidence interval (CI) 0.60 to 0.82; 12 studies, 4402 participants, unclear risk of bias), overall survival (HR 0.88, 95% CI 0.80 to 0.98; 12 studies, 4249 participants, low risk of bias) and tumour response rate (odds ratio (OR) 2.41, 95% CI 1.70 to 3.41; 12 studies, 4147 participants, unclear risk of bias). Of the 12 studies included in the comparison, 10 (eight with cetuximab, two with panitumumab) compared EGFR monoclonal antibodies and chemotherapy with the same chemotherapy alone, and two (one each with cetuximab and panitumumab) compared with best supportive care.

The PRIME study was an open-label, randomized, multicentre phase III trial which evaluated the efficacy and safety of panitumumab with FOLFOX versus FOLFOX alone as first-line treatment of patients with metastatic colorectal cancer and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (*9*). A total of 1183 patients were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus FOLFOX, or FOLFOX alone until disease progression or unacceptable toxicity. *KRAS* status was available for 1096 (93%) patients: 656/1096 (60%) had wild-type KRAS tumours and 440/1096 (40%) had mutant KRAS tumours. Outcome measures of progression-free and overall survival were analysed by *KRAS* status. In the KRAS wild-type subpopulation, addition of panitumumab to chemotherapy showed a significant improvement in progression-free survival (median progression-free survival 9.6 months versus 8.0 months; HR 0.80, 95% CI 0.66 to 0.97; $P = 0.02$). For overall survival, no significant difference was seen between treatment arms (median overall survival 23.9 months versus 19.7 months; HR 0.83, 95% CI 0.67 to 1.02; $P = 0.07$). In patients with mutant KRAS tumours, significant reductions were seen in both progression-free survival and overall survival in the panitumumab arm.

In a subsequent prospective–retrospective analysis of data from the PRIME study, the efficacy and safety of panitumumab plus FOLFOX versus FOLFOX alone, based on the *RAS* (*KRAS* or *NRAS*) or *BRAF* mutation status, were evaluated (*10*). Among 512 patients without *RAS* mutations, the addition of panitumumab was associated with significant improvements in progression-free survival (10.1 months versus 7.9 months; HR 0.72, 95% CI 0.58 to 0.90; $P = 0.04$) and overall survival (26.0 months versus 20.2 months; HR 0.78, 95% CI 0.62 to 0.99; $P = 0.04$). In patients without KRAS mutations, the addition of panitumumab was associated with a significant improvement in overall survival (median overall survival 23.8 months versus 19.4 months; HR 0.83, 95% CI 0.70 to 0.98; $P = 0.03$). Based on this study, panitumumab received a score of 4 on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (*11*).

Study 20050181 was a randomized phase III study that evaluated the efficacy and safety of panitumumab in combination with FOLFIRI versus FOLFIRI alone as second-line treatment of patients with metastatic colorectal cancer and ECOG performance of ≤ 2 (*12*). A total of 1186 patients were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus FOLFIRI or FOLFIRI alone. *KRAS* status was available for 1083 (91%) patients: 597/1083 (55%) had wild-type KRAS tumours, and 486/1083 (45%) had mutant KRAS tumours. Outcome measures of progression-free and overall survival were analysed by *KRAS* status. In the KRAS wild-type subpopulation, addition of panitumumab to chemotherapy showed a significant improvement in progression-free survival (median progression-free survival 5.9 months versus 3.9 months; HR 0.73, 95% CI 0.59 to 0.90; $P = 0.004$). For overall survival, no significant difference was seen between treatment arms (median overall survival 14.5 months versus 12.5 months; HR 0.85, 95% CI 0.70 to 1.04; $P = 0.12$). In patients with mutant KRAS tumours, no differences in efficacy were observed. Based on this study, panitumumab received a score of 3 on the ESMO-MCBS (*11*).

Study 20020007, an open-label, randomized, multicentre phase III study, evaluated the effect on overall survival of panitumumab plus best supportive care versus best supportive care alone in patients with chemorefractory KRAS or RAS wild-type metastatic colorectal cancer and ECOG performance status of ≤ 2 (*13*). Best supportive care was defined as investigator-judged best available palliative care. A total of 377 patients with wild-type KRAS exon 2 metastatic colorectal cancer were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus best supportive care or best supportive care alone. *RAS* status was available for 324 (86%) patients: 270/324 (83%) had wild-type RAS tumours and 54 (17%) had mutant KRAS tumours. The primary endpoint was overall survival in wild-type KRAS exon 2 metastatic colorectal cancer. A secondary endpoint was overall survival in wild-type RAS metastatic colorectal cancer. Patients were followed for survival for the later of either 24 months or until ~250 deaths were observed. For

patients with wild-type KRAS exon 2 tumours, a significant improvement was seen in overall survival for patients receiving panitumumab (median overall survival 10.0 months versus 7.4 months; HR 0.73, 95% CI 0.57 to 0.93; $P < 0.01$). Similarly, treatment with panitumumab also significantly improved overall survival in patients with wild-type RAS tumours (median overall survival 10.0 months versus 6.9 months; HR 0.70, 95% CI 0.53 to 0.93; $P = 0.01$). Progression-free survival was also significantly improved among patients receiving panitumumab (median progression-free survival 3.6 months versus 1.7 months; HR 0.51, 95% CI 0.41 to 0.64; $P < 0.0001$). No overall survival benefit from panitumumab was observed in patients with RAS mutations.

Comparison of panitumumab and bevacizumab

A 2024 systematic review and meta-analysis of eight trials (2624 participants) evaluated the efficacy and safety of first-line cetuximab or panitumumab plus FOLFOX or FOLFIRI versus bevacizumab plus doublet chemotherapy in patients with RAS wild-type left-sided, right-sided and all-sided metastatic colorectal cancer (*14*). Five of the trials reported outcomes by tumour sidedness. In the left-sided population, no significant difference was seen between treatment arms for progression-free survival (HR 0.93, 95% CI 0.84 to 1.04). For overall survival, a significant difference was found favouring EGFR inhibitors plus chemotherapy (HR 0.80, 95% CI 0.71 to 0.90). Similar results were seen in the all-sided population. In the right-sided population, significant improvement was seen in progression-free survival favouring bevacizumab plus chemotherapy (HR 1.45, 95% CI 1.19 to 1.78), while no significant difference between treatment arms was observed for overall survival (HR 1.17, 95% CI 0.95 to 1.44).

Summary of evidence: harms

The application stated that panitumumab is generally well tolerated, with most side-effects being manageable. Common adverse events include skin toxicities (such as rash), diarrhoea and electrolyte imbalances (hypomagnesaemia), in order of frequency. These toxicities are expected with EGFR inhibitors and can be mitigated with supportive care. Serious adverse effects, such as interstitial lung disease, are rare. Panitumumab does not cause significant myelosuppression.

In the 2017 Cochrane systematic review and meta-analysis, for the comparison of EGFR monoclonal antibodies added to standard therapy in patients with KRAS exon 2 wild-type metastatic colorectal cancer, pooled analysis of trials in first-, second- and third-line treatment settings found moderate-certainty evidence of an increased risk associated with the addition of EGFR monoclonal antibodies of: overall grade 3 to 4 toxicity (OR 2.45, 95% CI 2.07 to 2.89; six studies, 2771 participants); grade 3 to 4 diarrhoea (OR 1.84, 95% CI 1.47 to 2.32; seven studies, 2909 participants); grade 3 to 4 rash (OR 23.42, 95% CI 13.22 to

41.49; seven studies, 2909 participants); and grade 3 to 4 neutropenia (OR 1.22, 95% CI 0.93 to 1.61; six studies, 2666 participants) (*8*).

In the pivotal studies for panitumumab, adverse events of any grade were reported more frequently in patients receiving panitumumab than patients in the comparator arms. In the PRIME study, grade 3 to 4 adverse events occurring more frequently in the panitumumab arm and with >5% difference compared with the FOLFOX arm included skin toxicity, diarrhoea, fatigue, mucositis and hypomagnesaemia (*9*). In study 20050181, reported grade 3 to 4 adverse events were similar to those reported in the PRIME study (*12*). In study 20020007, adverse events of any grade with a ≥5% difference between treatment arms included rash, dermatitis acneiform and hypomangnesaemia (*13*).

Additional evidence

A 2023 systematic review and meta-analysis of two randomized controlled trials and two cohort studies (1436 participants) evaluated the benefits and safety of panitumumab (alone or in combination with chemotherapy) and cetuximab (alone or in combination with chemotherapy) for the treatment of KRAS wild-type metastatic colorectal cancer (*15*). Meta-analysis of pooled data found no significant differences between treatments for progression-free survival (HR 0.92, 95% CI 0.83 to 1.02), overall survival (HR 0.91, 95% CI 0.81 to 1.03) or response rate (HR 1.22 95% CI 0.96 to 1.61). In terms of safety, no significant differences were seen between groups in the incidence of acneiform rash, severe acneiform rash, diarrhoea or severe diarrhoea. In the panitumumab arm, a significantly lower incidence of paronychia was seen, while in the cetuximab arm, significantly lower incidences of hypomagnesaemia and severe hypomagnesaemia were observed.

The ASPECCT study was a randomized, multicentre, open-label phase III non-inferiority trial comparing panitumumab and cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer and EGOC performance of ≤2 (*16*). A total of 999 patients were randomized in a 1:1 ratio to receive panitumumab 6 mg/kg every 2 weeks or cetuximab 400 mg/m2 initially, followed by 250 mg/m2 every week until disease progression, intolerability, or withdrawal of consent. In the primary analysis of overall survival, panitumumab was reported to be non-inferior to cetuximab. Median overall survival in the panitumumab and cetuximab arms were 10.4 months and 10.0 months, respectively (HR 0.97, 95% CI 0.84 to 1.11). Panitumumab retained 105.7% of the effect of cetuximab of overall survival seen in this study, meeting the predefined non-inferiority criteria. The incidence of adverse events between treatment arms was similar, including any grade and grade 3 or4. Grade 3 or4 skin toxicity occurred in 13% and 10% of patients treated with panitumumab and cetuximab, respectively. In patients receiving panitumumab, there was a lower occurrence of grade 3 or 4 infusion reactions, but a higher occurrence of grade 3 or 4 hypomagnesaemia.

WHO guidelines

WHO guidelines for the treatment of metastatic colorectal cancer are not currently available.

Guidelines for metastatic colorectal cancer from the National Comprehensive Cancer Network (NCCN) (*17*), the European Society for Medical Oncology (*18*), and the American Society of Clinical Oncology (*19*) include recommendations for the use of panitumumab or cetuximab as part of first-, second- or later-line treatment of KRAS/NRAS wild-type metastatic colorectal cancer. In first-line therapy, these medicines are recommended in combination with chemotherapy, while in later lines, they may be used as monotherapy or in combination with chemotherapy.

Costs/cost–effectiveness

The application presented a summary of available list price information for panitumumab. Among high-income countries, list prices for the 100 mg (400 mg) vials ranged from 277 United States dollars (US$) (US$ 1109) in Taiwan, China to US$ 750 (US$ 3000) in Kuwait. In upper middle-income countries, list prices for the 100 mg (400 mg) vials ranged from US$ 228 (US$ 912) in South Africa to US$ 11 354 (US$ 45 416) in Argentina. In lower middle-income countries, list prices for the 100 mg (400 mg) vials ranged from US$ 120 (US$ 480) in Egypt to US$ 447 (US$ 1788) in Morocco.

A 2014 study evaluated the cost–effectiveness of panitumumab plus modified FOLFOX6 versus bevacizumab plus modified FOLFOX6 as first-line treatment of patients with RAS wild-type metastatic colorectal cancer from a French health-care system perspective (*20*). Based on efficacy outcomes from the PEAK study which showed better efficacy outcomes for people treated with panitumumab plus FOLFOX6 versus those treated with bevacizumab plus FOLFOX6, the incremental costs per life year gained and per quality-adjusted life year (QALY) were 26 918 euros (€) and €36 577, respectively. The authors concluded that compared with bevacizumab treatment, panitumumab treatment represented good value for money and could be considered cost-effective in France at a willingness-to-pay threshold of between €40 000 and €60 000.

A similar study evaluated the cost–effectiveness of panitumumab plus modified FOLFOX6 versus bevacizumab plus modified FOLFOX6 as first-line treatment of patients with RAS wild-type metastatic colorectal cancer from a Greek health-care system perspective (*21*). The incremental cost–effectiveness ratio of panitumumab treatment was €34 664 per QALY. Probabilistic sensitivity analysis found that the probability of panitumumab treatment being cost-effective over bevacizumab treatment was 81.5% at the predetermined threshold of €51 000 per QALY gained.

A 2013 study from the United Kingdom of Great Britain and Northern Ireland evaluated the clinical effectiveness and cost–effectiveness of panitumumab monotherapy and cetuximab (mono- or combination chemotherapy) for treatment of KRAS wild-type metastatic colorectal cancer, and bevacizumab in combination with non-oxaliplatin chemotherapy for treatment of metastatic colorectal cancer after first-line chemotherapy (*22*). The economic evaluation included five studies. The base-case incremental cost–effectiveness ratio was: 98 000 pounds sterling (£) per QALY for cetuximab in KRAS wild-type patients compared with best supportive care; £150 000 per QALY for panitumumab compared with best supportive care; and £88 000 per QALY or cetuximab plus irinotecan compared with best supportive care. The authors concluded that although cetuximab and panitumumab appear to be clinically beneficial for patients with KRAS wild-type metastatic colorectal cancer compared with best supportive care, they are likely to represent poor value for money when judged by cost–effectiveness criteria currently used in the United Kingdom.

Availability

Panitumumab has regulatory approval for use in the treatment of metastatic colorectal cancer in more than 50 countries globally.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of panitumumab on the EML for treatment of adults with KRAS/NRAS wild-type metastatic colorectal cancer. The group judged that the magnitude of the overall survival gains were moderate in the first-line setting, and below the recommended threshold of 4–6 months in the second- and third-line settings. The group also highlighted the need for RAS mutation testing to identify patients with RAS mutations, given that the addition of panitumumab to chemotherapy in this population is associated with decreased overall survival compared with chemotherapy alone.

Committee recommendations

The Expert Committee recognized the substantial and increasing burden of metastatic colorectal cancer, particularly in low- and middle-income countries. The Committee noted that survival outcomes are worse in these settings as patients typically present in more advanced disease stages, in part due to limited screening programmes and limited access to effective diagnostic infrastructure. After diagnosis, access to surgery, chemotherapy and radiotherapy is constrained by resource limitations and workforce shortages.

In consideration of the evidence for benefits and harms, the Committee noted that overall survival benefit of panitumumab plus chemotherapy over

chemotherapy alone in the second-line setting, and of panitumumab over best supportive care in the third-line setting was limited and below the established EML threshold of at least 4–6 months overall survival gain. The Committee considered the benefit of panitumumab plus chemotherapy over chemotherapy alone in the first-line setting was modest. Furthermore, the benefit appeared inconsistent in different patient subpopulations. Factors such as tumour location and additional *RAS/BRAF* mutations have been proposed as predictors of panitumumab efficacy. The Committee noted that the role of primary tumour location (right- versus left-sided) was a less definitive predictor: left-sided tumours respond better to anti-EGFR therapy than right-sided tumours. However, the effect is not absolute and is also influenced by RAS/BRAF mutation status..

The Committee noted that in patients with metastatic colorectal cancer with *RAS* mutations, the addition of panitumumab to chemotherapy was associated with a decrease in overall survival. Thus, the Committee emphasized the need to identify *RAS* mutation status and exclude patients with *RAS* mutations from receiving panitumumab. The Committee considered that limited access to the required diagnostic testing in resourced-constrained settings was likely to be an important barrier to appropriate and safe use of panitumumab.

The Committee also noted that panitumumab was associated substantial risk of harms and showed no meaningful improvement in quality of life in most studies.

Based on these considerations, the Expert Committee did not recommend the inclusion of panitumumab on the EML for the treatment of KRAS wild-type metastatic colorectal cancer.

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Zanubrutinib – addition – EML

Zanubrutinib **ATC code: L01EL03**

Proposal

Addition of zanubrutinib to the complementary list of the EML for the treatment of adults with treatment naïve or relapsed/refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).

Applicant

BieGene Ltd, Cambridge, MA, United States of America

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical department supported deferring the inclusion of zanubrutinib on the EML until further evidence for overall survival benefit and safety are available.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Capsule: 80 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Applications for the inclusion of zanubrutinib for the treatment of CLL/SLL have been considered by the Expert Committee on two previous occasions in 2021 and 2023 (*1*). On each occasion, listing was not recommended.

With the 2023 application, the Expert Committee acknowledged the role of targeted therapy with Bruton kinase inhibitors in the treatment of CLL/SLL, especially in high-income countries, The 2023 Committee recalled the

recommendation of the 2021 Committee to include ibrutinib on the EML for patients with relapsed/refractory disease as there was compelling evidence of relevant benefit and improved tolerability compared with chemoimmunotherapy.

The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine–rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, which showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited and noted that few long-term data were currently available. The Committee also noted the toxicity concerns highlighted by the Cancer Medicines Working Group and considered longer-term data would be informative to confirm the safety profile of zanubrutinib.

The Committee also noted the high price of zanubrutinib and considered that at this price, it was unlikely to be cost-effective or affordable in most low- and middle-income settings. The Committee also considered that the substitution of ibrutinib with zanubrutinib would not necessarily be associated with savings in health budgets as proposed in the application because lower ibrutinib doses than those described in the application could be used in clinical practice (*1*).

Public health relevance

The global incidence of CLL/SLL increased from 40 537 in 1990 to 103 467 in 2019, with age-standardized incidence rates rising from 0.76 per 100 000 people in 1990 to 1.34 per 100 000 people in 2019. In 2019, the highest age-standardized incidence rates were reported in western Europe, North America and central Europe. Globally, almost 45 000 deaths due to the disease occurred in 2019 (*2*).

Summary of evidence: benefits

Systematic reviews

A 2024 systematic review and meta-analysis of 15 prospective studies (10 single-arm studies and five randomized controlled trials; 2066 participants) evaluated the efficacy and safety of acalabrutinib, zanubrutinib and tirabrutinib, alone or in combination with other regimens for treatment-naïve and relapsed/refractory CLL/SLL (*3*). Some studies included more than one disease state or intervention, resulting in 20 studies being evaluated – 12 involving acalabrutinib, seven involving zanubrutinib and one involving tirabrutinib. Efficacy endpoints assessed were overall response rate, complete response rate, 24-month overall survival and progression-free survival rates. The pooled 24-month overall survival rate for CLL patients treated with Bruton tyrosine kinase inhibitors was 94% (95% confidence interval (CI) 92% to 97%; $P = 0.06$). Subgroup analyses for acalabrutinib monotherapy and zanubrutinib monotherapy showed pooled 24-month overall survival rates of 92% (95% CI 89% to 96%) and 95% (95% CI 92% to 96%; $P = 0.72$), respectively. The 24-month progression-free survival rates were

86% (95% CI 82% to 90%) for Bruton tyrosine kinase inhibitors, 83% (95% CI 75% to 90%) for acalabrutinib and 86% (95% CI 80% to 91%) for zanubrutinib.

Pooled overall response rate and complete response rate for Bruton tyrosine kinase inhibitors were 92% (95% CI 89% to 95%) and 10% (95% CI 6% to 14%), respectively. Subgroup analyses by disease status in treatment-naïve patients showed pooled overall response rate and complete response rate of 96% (95% CI 92% to 98%) and 16% (95% CI 7% to 28%), respectively. In patients with relapsed/refractory disease, pooled overall response rate and complete response rate were 90% (95% CI 85% to 95%) and 7% (95% CI 4% to 10%), respectively. The overall response rate and complete response rate were 87% (95% CI 81% to 93%) and 3% (95% CI 1% to 6%), respectively, for acalabrutinib monotherapy and 93% (95% CI 89% to 97%) and 13% (95% CI 6% to 22%), respectively, for zanubrutinib monotherapy.

Clinical studies

The SEQUOIA trial was an open-label, multicentre, phase III trial comparing zanubrutinib and bendamustine–rituximab in patients with previously untreated CLL/SLL (*4*). Patients without 17p deletion (del(17p13·1)) were randomly assigned to receive zanubrutinib (group A) or bendamustine–rituximab (group B). Patients with del(17p13.1) were enrolled in group C and received zanubrutinib. Administered doses were: zanubrutinib 160 mg orally twice daily (28-day cycles); bendamustine 90 mg/m2 intravenous on days 1 and 2 for six cycles plus rituximab 375 mg/m^2 intravenous the day before or on day 1 of cycle 1, and 500 mg/m^2 intravenous on day 1 of cycles 2–6. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat population in groups A and B. With median follow-up of 26.2 months, zanubrutinib showed a statistically significantly reduced risk of disease progression (hazard ratio (HR) 0.42, 95% CI 0.28 to 0.63). Zanubrutinib had a longer progression-free survival compared with bendamustine–rituximab in most patient subgroups. After 42 months of median follow-up, the progression-free survival benefit of zanubrutinib over bendamustine-rituximab was sustained (HR 0.30, 95% CI 0.21 to 0.43). Estimated 42-month progression-free survival rates were 82.4% and 50.0%, respectively. Median overall survival was not reached in either treatment arm (*5*). In group C, with median follow-up of 30.5 months, median progression-free survival was not reached. Estimated 24-month progression-free survival and overall survival for zanubrutinib was 88.9% and 93.6%, respectively (*4*). After 42 months of median follow-up, median progression-free survival and overall survival were not reached. The 42-month event-free rates were 79.4% for progression-free survival and 89.5% for overall survival (*5*).

An interim analysis of health-related quality of life outcomes was assessed using patient-reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L visual analogue

scale (VAS) (6). Patients treated with zanubrutinib showed greater improvements in health-related quality of life at weeks 12 and 24 compared with patients treated with bendamustine–rituximab. At 24 weeks, these differences were significantly higher for zanubrutinib in global health status, physical functioning, role functioning, and reduction in diarrhoea, fatigue and nausea/vomiting.

The ALPINE trial was a randomized phase III trial comparing the efficacy and safety of zanubrutinib with ibrutinib in patients with relapsed/refractory CLL/SLL (7). Patients were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg daily. After a median follow-up of 29.6 months, zanubrutinib was superior to ibrutinib for progression-free survival among 652 patients as assessed by investigators (HR for disease progression or death, 0.65, 95% CI 0.49 to 0.86). The results were similar for progression-free survival assessed by an independent review committee (HR 0.63, 95% CI 0.48 to 0.84). At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib group and was 34.2 months (95% CI 33.3 to not estimable) in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (HR 0.53, 95% CI 0.31 to 0.88). Progression-free survival across other major subgroups consistently favoured zanubrutinib. At the data-cut-off date in the final analysis, results for overall survival showed fewer deaths in the zanubrutinib group than in the ibrutinib group (48 versus 60; HR for death 0.76, 95% CI 0.51 to 1.11). Median overall survival was not reached in either treatment arm. In the final analysis of the intention-to-treat population, overall response rates as assessed by the investigators were 83.5% in the zanubrutinib group and 74.2% in the ibrutinib group. The overall response rate as assessed by the independent review committee was 86.2% in the zanubrutinib group and 75.7% in the ibrutinib group.

After a median follow-up of 42.5 months, the progression-free survival benefit of zanubrutinib over ibrutinib was sustained (HR 0.68, 95% CI 0.54 to 0.84). Progression-free survival rates at 36 months were 65.4% and 54.4% in the zanubrutinib and ibrutinib groups, respectively. The progression-free survival benefit was also sustained in patients with (HR 0.51, 95% CI 0.33 to 0.78) and without (HR 0.79, 95% CI 0.61 to 1.02) 17p deletion/TP53 mutation, and in most other major subgroups and sensitivity analyses. Overall response rates were higher in the zanubrutinib group than in the ibrutinib group (85.6% versus 75.4%; response ratio (RR) 1.13, 95% CI 1.05 to 1.22). Median overall survival was not reached in either treatment group. There were 69 and 85 deaths in the zanubrutinib and ibrutinib groups, respectively (HR for overall survival 0.77, 95% CI 0.55 to 1.06) (8).

Quality of life was measured using EORTC QLQ-C30 and EQ-5D-5L questionnaires (*9*). Patients receiving zanubrutinib experienced improvements in physical and role functioning, pain and fatigue in the EORTC QLQ-C30. Zanubrutinib-treated patients also reported lower diarrhoea scores. In the EQ-5D-5L, the mean change from baseline in EQ-VAS showed greater improvement in patients receiving zanubrutinib than patients receiving ibrutinib (mean change (standard deviation) 7.92 (18.245) versus 3.44 (16.972).

Study BGB-3111-205 was a single-arm, open-label phase II study evaluating safety and efficacy of zanubrutinib in relapsed/refractory CLL/SLL (*10*). After a median follow-up of almost 34 months, investigator-assessed overall response rate was 87.9%, with 6.6% of patients achieving a complete response, 69.2% achieving a partial response, and 12.1% achieving a partial response with lymphocytosis. The overall response rate was generally consistent across all subgroups analysed, including patients with high-risk cytogenetics (*11*).

Study BGB-3111-AU-003 was a phase I/II open-label, multiple dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of zanubrutinib in patients with B-cell lymphoid malignancies, including 22 patients with treatment-naïve CLL/SLL and 101 patients with relapsed/refractory CLL/SLL (*12*). Patients received zanubrutinib 160 mg twice daily ($n = 81$), 320 mg once daily ($n = 40$) or 160 mg once daily ($n = 2$). After a median follow-up of 47.2 months, the overall response rate was 95.9% (100% for treatment naïve patients, and 95% relapsed/refractory), with 18.7% achieving complete response. Ongoing response at 3 years was reported in 85.7% of patients. The overall response rate in patients with 17p deletion)/TP53 mutation was 87.5%. The 2- and 3-year estimated progression-free survival was 90% (treatment naïve 90%; relapsed/refractory 91%) and 83%, respectively.

Real-world studies

The results of a retrospective study that evaluated real-world switching and sequencing to next line of therapy in patients starting a Bruton tyrosine kinase inhibitor as first- or second-line treatment of SLL/CLL were published in an abstract in 2024 (*13*). A total of 2816 and 1253 patients started a first- or second-line Bruton tyrosine kinase inhibitor, respectively, during the study period. First-line were 157 with zanubrutinib, 1238 with acalabrutinib and 1421 with ibrutinib; second-line were 107 with zanubrutinib, 672 with acalabrutinib, and 474 with ibrutinib. Median follow-up for the first-line was 123 days for zanubrutinib, 406 days for acalabrutinib and 637 days for ibrutinib. Regardless of the line of therapy, zanubrutinib-treated patients had a significantly lower switching rate within 90 days and a lower proportion of patients receiving next line of therapy at 180 days compared with acalabrutinib and ibrutinib.

Summary of evidence: harms

Systematic reviews

A 2024 systematic review and network meta-analysis of 10 randomized controlled trials (4171 participants) evaluated the safety profile of first-line targeted therapies (acalabrutinib, ibrutinib, obinutuzumab, ofatumumab, venetoclax and zanubrutinib) in an unfit subpopulation of elderly and/or comorbid CLL patients (*14*). The results of the network meta-analysis showed that ibrutinib + venetoclax was associated with a significantly higher risk of adverse events leading to treatment discontinuation than other evaluated therapies: versus zanubrutinib (odds ratio (OR) 16.50, 95% credible interval (CrI) 2.73 to 153.68); versus acalabrutinib (OR 12.56, 95% CrI 5.28 to 102.70); versus chlorambucil + obinutuzumab (OR 9.62, 95% CrI 20.2 to 78.15); versus acalabrutinib + obinutuzumab (OR 9.62, 95% CrI 2.02 to 78.15); and versus venetoclax + obinutuzumab (OR 6.67, 95% CrI 1.46 to 52.55). No significant differences were found between the remaining targeted therapies. Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome based on surface under the cumulative ranking curves (SUCRA 86%). Adverse events of grade ≥ 3 were generally significantly more frequent in groups treated with combination therapies than monotherapy. Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome (SUCRA 98%). Serious adverse events (any grade) were significantly less frequent with zanubrutinib than ibrutinib (OR 0.35, 95% CrI 0.20 to 0.59), acalabrutinib (OR 0.38, 95% CrI 0.17 to 0.85), ibrutinib + obinutuzumab (OR 0.25, 95% CrI 0.11 to 0.57), ibrutinib + rituximab (OR 0.39, 95% CrI 0.22 to 0.67), ibrutinib + venetoclax (OR 0.28, 95% CrI 0.12 to 0.66) and acalabrutinib + obinutuzumab (OR 0.28, 95% CrI 0.13 to 0.62). Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome (SUCRA 95%). The most frequently reported haematological adverse events were anaemia, thrombocytopenia, neutropenia and febrile neutropenia. Grade 1–5 anaemia was significantly less frequent with zanubrutinib than with chlorambucil + obinutuzumab, and acalabrutinib. No significant differences were observed between zanubrutinib and other investigated treatments for grade 1–5 anaemia. The risk of neutropenia was significantly lower for Bruton tyrosine kinase inhibitor monotherapy, particularly zanubrutinib and acalabrutinib. The rate of febrile neutropenia (any grade) was significantly lower for acalabrutinib compared with chlorambucil + obinutuzumab, but no significant differences were observed between other investigated therapies.

The results of a 2023 systematic review and meta-analysis of 61 trials (6959 participants) that evaluated treatment-emergent adverse events of ibrutinib, acalabrutinib and zanubrutinib reported in clinical trials in B-cell malignancies were published as a conference poster (*15*). Most trials were in CLL/SLL ($n = 36$),

mantle cell lymphoma ($n = 9$) or Waldenström macroglobulinaemia ($n = 8$). Compared with ibrutinib, the average incidence of all-grade adverse events was lower with acalabrutinib (relative risk (RR) 0.74, 95% CrI 0.62 to 0.85) and zanubrutinib (RR 0.83, 95% CrI 0.71 to 0.93). Similarly, compared with ibrutinib, the incidence of grade ≥ 3 adverse events was lower for both acalabrutinib and zanubrutinib. Zanubrutinib and acalabrutinib had similar average incidences of grade ≥ 3 adverse events. Grade ≥ 3 adverse events that occurred more frequently with acalabrutinib than zanubrutinib included anaemia (RR 0.58), infections (RR 0.76) and rash (RR 0.03). Grade ≥ 3 adverse events that occurred more frequently with zanubrutinib than acalabrutinib included cellulitis (RR 6.6), upper respiratory tract infection (RR 2.09) and neutropenia (RR 1.43).

In the 2024 systematic review and meta-analysis that evaluated the efficacy and safety of acalabrutinib, zanubrutinib and tirabrutinib, alone or in combination with other treatments, for treatment-naïve and relapsed/refractory CLL/SLL, pooled rates of grade ≥ 3 neutropenia, anaemia and thrombocytopenia in acalabrutinib monotherapy were 14%, 7% and 5%, respectively. The pooled rates of grade ≥ 3 neutropenia, thrombocytopenia and anaemia in zanubrutinib monotherapy were 19%, and 4% and 2%, respectively. Zanubrutinib monotherapy had a similar pooled rate of grade ≥ 3 upper respiratory tract infection (2% versus 1%) and grade ≥ 3 hypertension (6% versus 4%) compared with acalabrutinib monotherapy (*3*).

Clinical studies

In the SEQUOIA trial, grade ≥ 3 adverse events were reported in 126 (52.5%) and 181 (79.7%) participants in the zanubrutinib and bendamustine–rituximab arms, respectively. Serious adverse events were reported in 88 (36.7%) and 113 (49.8%) participants, respectively. The most frequently reported grade ≥ 3 adverse events in the zanubrutinib arm were infections (16.3%), neutropenia (11.7%), other cancers (7.1%), hypertension (6.3%) and bleeding and major bleeding (both 3.8%). The most frequently reported grade ≥ 3 adverse events in the bendamustine–rituximab arm were neutropenia (51.1%), infections (18.9%), thrombocytopenia (7.9%) and hypertension (4.8%). Adverse events leading to treatment discontinuation were 8% and 14% in the zanubrutinib and bendamustine-rituximab arms, respectively (*4*).

In the ALPINE trial, treatment discontinuation was lower with zanubrutinib (26.3%) than ibrutinib (41.2%), with most discontinuations due to adverse events (16.2% versus 22.8%) or progressive disease (7.3% versus 12.9%). A lower incidence of cardiac adverse events was reported in the zanubrutinib than the ibrutinib groups (21.3% versus 29.6%), with discontinuation due to cardiac disorders reported in 0.3% versus 4.3% of participants receiving zanubrutinib and ibrutinib, respectively. The rate of atrial fibrillation/flutter was lower with

zanubrutinib than ibrutinib (any grade 5.2% versus 13.3%; grade ≥3 2.5% versus 4.0%). Neutropenia of any grade was reported in 29.3% and 24.4% in the zanubrutinib and ibrutinib groups, respectively. Incidences of neutropenia and febrile neutropenia of grade ≥3 were similar in the two groups. The incidence of infections were similar between treatment groups (any grade: 71.3% versus 73.1%; grade ≥3: 26.5% versus 28.1%). The incidence of hypertension (all grades and grade ≥3) was also similar between treatment groups (*7*).

At 42.5 months median follow-up of the ALPINE trial, the most common non-haematological treatment-emergent adverse events of any grade with zanubrutinib versus ibrutinib were infections related to coronavirus disease 2019 (COVID-19) (46.0% versus 33.3%), upper respiratory tract infection (29.3% versus 19.8%), hypertension (27.2% versus 25.3%) and diarrhoea (18.8% versus 25.6%). The most commonly reported non-haematological grade ≥3 adverse events were COVID-19-related infections (17.9% versus 12.0%), hypertension (17.0% versus 16.0%) and pneumonia (7.7% versus 10.5%), respectively. Neutropenia was the most common haematological adverse event of any grade (31.5% versus 29.6%) and grade ≥3 (22.8% versus 22.8%) with zanubrutinib and ibrutinib, respectively; febrile neutropenia was reported as 1.2% in both arms (*8*).

In study BGB-3111-AU-003, the most frequently reported treatment-emergent adverse events (any grade) were infections (86.2%), contusions (52.0%), and cough and diarrhoea (both 35.8%). Grade ≥3 neutropenia was reported in 20.3% of participants. Twelve participants (9.7%) discontinued treatment due to adverse events (*12*).

Study BGB-3111-215 was a phase II open-label, single-arm study that evaluated zanubrutinib in 67 patients with B-cell malignancies in the United States who were intolerant to prior treatment with ibrutinib and/or acalabrutinib (*16*). After a median follow-up of 12 months, 70% and 83% of ibrutinib- and acalabrutinib-intolerant adverse events, respectively, did not recur with treatment with zanubrutinib. Among recurring adverse events, 7/34 (21%) ibrutinib intolerance events and 2/3 (67%) acalabrutinib intolerance events recurred at the same severity with zanubrutinib, while the remainder recurred at a lower severity.

Real-world studies

Results of a retrospective study that evaluated real-world treatment patterns based on a formulary change from ibrutinib to zanubrutinib in patients in a community oncology practice in the United States were published in an abstract in 2024 (*17*). Of 281 patients who received zanubrutinib, 190 had switched from ibrutinib and 91 received only zanubrutinib. The primary reasons for switching to zanubrutinib were formulary change (73%) and disease progression (15%). Similar rates of treatment-emergent adverse events were seen with use of both therapies, with lower rates of treatment-limiting adverse events seen with zanubrutinib. The

most common treatment-limiting adverse events were atrial fibrillation and fatigue with ibrutinib, and cytopenias and rash/bruising with zanubrutinib. Rates of cardiac adverse events were higher with ibrutinib, however rates decreased after switching from ibrutinib to zanubrutinib. Dose modification occurred in 34 patients treated with ibrutinib and in 50 patients treated with zanubrutinib.

The results of a retrospective observational study that evaluated real-world cardiovascular adverse events, time to treatment discontinuation and time to next treatment in patients with CLL/SLL treated with Bruton tyrosine kinase inhibitors in the United States were published in an abstract in 2024 (*18*). In total, 3064 patients started a Bruton tyrosine kinase inhibitor as first- or later-line treatment during the study period (1389 on ibrutinib, 1223 on acalabrutinib, and 203 on zanubrutinib). Median follow-up was 20.5 months, 14.2 months and 6 months, for ibrutinib, acalabrutinib and zanubrutinib, respectively. Significantly more patients who received ibrutinib first-line experienced cardiovascular adverse events than those receiving acalabrutinib or zanubrutinib at 3, 6 and 9 months follow-up. The proportions of patients continuing treatment and the median time to next treatment was longer for patients who received zanubrutinib. Of patients treated with first-line ibrutinib, 12.7% discontinued and switched to a second-generation Bruton tyrosine kinase inhibitor. The median time to treatment discontinuation in the first-line setting was 13.7 months for ibrutinib, 19.2 months for acalabrutinib and 19.3 months for zanubrutinib. The associated probabilities of continuing the same treatment were higher with zanubrutinib (81.6%) than with ibrutinib (64.8%) or acalabrutinib (64.8%) at 6 months. In the first-line setting, the median time to next treatment was not reached for zanubrutinib and was 30.2 months for ibrutinib and 35.8 months for acalabrutinib.

Additional evidence

Median 5-year follow-up data from the SEQUOIA trial showed that median progression-free survival was not reached in the zanubrutinib group and was 44.1 months in the bendamustine–rituximab group (HR 0.29, 95% CI 0.21 to 0.40). The estimated 60-month progression-free survival for zanubrutinib and bendamustine–rituximab was 75.8% and 40.1%, respectively. Median overall survival was not reached in either treatment arm (HR 0.89, 95% CI 0.55 to 1.43) and the estimated 60-month overall survival rates were 85.8% and 85.0% in the zanubrutinib and bendamustine–rituximab arms, respectively (*19*).

WHO guidelines

WHO guidelines for the treatment of CLL/SLL are not currently available.

Recommendations for the use of zanubrutinib as first- and later-line therapy of CLL/SLL are included in various national and international guidelines (*20*–*22*).

Costs/cost–effectiveness

Information on the cost of zanubrutinib in different settings was not presented in the application.

The application identified six economic evaluation studies involving zanubrutinib in the treatment of CLL/SLL.

A 2024 cost–utility analysis evaluated the cost–effectiveness of zanubrutinib versus ibrutinib in relapsed or refractory CLL from the commercial payer perspective in the United States based on survival curves from the ALPINE trial (*23*). Over a 10-year time horizon, the incremental cost–effectiveness ratio of zanubrutinib versus ibrutinib was 91 260 United States dollars (US$) per life-year gained and US$ 120 634 per quality-adjusted life-year (QALY) gained. Incremental cost–effectiveness ratios were considered cost-effective at a threshold of US$ 150 000 per QALY gained. The incremental cost–effectiveness ratio was most sensitive to drug acquisition costs and progression-free survival distributions. The probability of zanubrutinib being cost-effective was reported to be about 52.8%, with a 30.0% likelihood of dominance.

The results from a cost-minimization analysis of zanubrutinib, acalabrutinib and ibrutinib in the treatment of relapsed/refractory CLL were published in an abstract in 2023 (*24*). The analysis used a three health-state (progression free, progressive disease, death) partitioned survival model from a United Kingdom National Health Service payer perspective over a lifetime time horizon. The model assumed equal efficacy of zanubrutinib, ibrutinib and acalabrutinib. Zanubrutinib was associated with cost savings of 7802 pounds sterling (£) per person versus acalabrutinib and an incremental cost of £19 677 per person versus ibrutinib. Acalabrutinib was associated with an incremental cost of £27 478 per person versus ibrutinib. Differences in treatment acquisition costs were the key reason for the cost differences between treatments. Zanubrutinib was associated with fewer management costs for adverse events than acalabrutinib and ibrutinib.

A 2024 model-based study evaluated the cost–effectiveness of zanubrutinib and ibrutinib in relapsed and refractory CLL from the payer perspective in China and the United States (*25*). For Chinese payers, zanubrutinib had superior cost–effectiveness compared with ibrutinib, with an incremental cost–effectiveness ratio of US$ −88 068 per QALY. Zanubrutinib was a more affordable option for the United States, with an incremental cost–effectiveness ratio of US$ −284 485 per QALY.

The results from a 2023 study comparing zanubrutinib and ibrutinib in relapsed/refractory CLL by calculating the number needed to treat to avoid one progression or death and associated incremental costs from a United States payer perspective were published as a conference poster abstract (*26*). Modelled results in the base case showed a number needed to treat of 8 for zanubrutinib compared

with using ibrutinib. The total costs per patient treated were US$ 370 558 and US$ 430 150 for zanubrutinib and ibrutinib, respectively, with cost savings of US$ 59 593 associated with the use of zanubrutinib.

The results from a 2022 budget impact analysis of zanubrutinib for the treatment of relapsed/refractory CLL from a United States payer perspective were published in an abstract (*27*). The modelled analysis compared a reference scenario with the current market mix (i.e. before the introduction of zanubrutinib) and a revised market mix in which uptake of zanubrutinib was included. The base-case analysis of a hypothetical 1-million-member health plan in which two patients were estimated to have relapsed/refractory CLL and started treatment showed that total health-care costs over 1 year were US$ 426 000 with zanubrutinib and US$ 430 000 without zanubrutinib, suggesting that adding zanubrutinib was associated with cost savings. One-way sensitivity analysis results showed that the budget impact on health-care costs over a 1-year time horizon were most sensitive to the zanubrutinib wholesale acquisition cost.

The results from another 2022 budget impact analysis of zanubrutinib for treatment-naïve CLL/SLL from a United States payer perspective were published in an abstract (*28*). In a hypothetical health plan with 1 million members, 31 patients were estimated to receive active first-line treatment each year for CLL/SLL. Base-case scenarios of clinical practice with and without zanubrutinib were estimated. Total health-care costs were US$ 37.75 million with zanubrutinib and US$ 37.84 million without zanubrutinib. Over a 3-year time-horizon, the overall budget impact was a reduction of US$ 82 437, representing a 0.22% cost-saving with the use of zanubrutinib. Sensitivity analysis indicated that drug costs, payer perspective and treatment duration had the greatest impact on the financial budget of health-care costs.

Availability

Zanubrutinib has regulatory approval in 40 countries/jurisdictions globally for use in the treatment of treatment-naïve and/or relapsed/refractory CLL/SLL. Most of these countries/jurisdictions are upper middle- and high-income settings.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of zanubrutinib on the EML for treatment of adults with treatment-naïve or relapsed/refractory CLL/SLL. The group noted that treatment for CLL/SLL is a rapidly evolving field, with ongoing studies evaluating combination regimens with zanubrutinib. Furthermore, while available data demonstrate better progression-free survival gains with zanubrutinib than ibrutinib, data for overall survival are less convincing. The group also considered that the improved safety profile of

zanubrutinib versus ibrutinib was likely to be the effect of the comparison with the approved dose of ibrutinib. They noted that post-approval studies suggest that lower ibrutinib doses are as effective and that ibrutinib was therefore used at a dose that was too high, likely leading to an overestimate of the difference in adverse events.

Committee recommendations

The Expert Committee recognized the growing global burden of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), with incidence rates rising significantly over the past 30 years, particularly in high-income countries. The Committee also recognized that treatment of CLL/SLL with Bruton tyrosine kinase inhibitors is now considered the standard of care in many countries, replacing chemo-immunotherapy.

The Committee recalled that another Bruton tyrosine kinase inhibitor, ibrutinib, was included on the EML in 2021 for use in relapsed/refractory CLL/SLL based on evidence of greater benefit and improved tolerability compared with chemo-immunotherapy.

In consideration of the available evidence for zanubrutinib, the Committee considered that the evidence in relapsed/refractory disease demonstrated a survival advantage for zanubrutinib compared with chemo-immunotherapy, and similar survival to that previously observed for ibrutinib. Additionally, zanubrutinib appears to be associated with more favourable safety compared with ibrutinib (e.g. less atrial fibrillation and bleeding adverse events in some trials). The Committee considered that zanubrutinib offered a clinically meaningful alternative to ibrutinib in the relapsed/refractory setting.

In the first-line setting, the Committee considered that the available evidence for the benefit of zanubrutinib was promising but not yet as well established as in the relapsed/refractory setting.

While no specific price data were provided in the application, the Committee acknowledged the high price of zanubrutinib in different settings. Economic analyses in different settings have reported varying outcomes, with cost–effectiveness often being sensitive to drug acquisition costs. The Committee also acknowledged that ibrutinib is still highly priced in most countries. The Committee considered that ibrutinib may face competition from newer agents within the class such as zanubrutinib, which is more accessible in some countries, has a better domestic cost–effectiveness profile and could potentially better align with local medicine policy priorities.

The Committee noted that not all patients with CLL/SLL require treatment. At diagnosis, many patients have indolent, asymptomatic disease that does not benefit from therapy, and some patients may never require treatment. Criteria that identify clinical and biological states when treatment are indicated

(i.e. provides symptom resolution or prolongs life) were well established in the chemo-immunotherapy era and are still applicable for targeted therapies such as Bruton tyrosine kinase inhibitors. To avoid net harm and unnecessary cost, the Committee emphasized that the use of Bruton tyrosine kinase inhibitors, including zanubrutinib, must be restricted to use within guidelines. This is likely to be a main factor in consideration of affordability of this class of medicines in low- and middle-income countries.

Based on these considerations, the Expert Committee recommended the inclusion of zanubrutinib on the EML for the treatment of relapsed or refractory CLL/SLL as a therapeutic alternative to ibrutinib (which remains the representative Bruton tyrosine kinase inhibitor) under a square box listing.

The Committee did not recommend the inclusion of zanubrutinib for use in the first-line treatment of CLL/SLL but encouraged an application presenting evidence for the class of Bruton tyrosine kinase inhibitors be submitted for consideration in the 2027 update.

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8.2.3 Immunomodulators

Blinatumomab – addition – EMLc

Blinatumomab	ATC code: L01FX07

Proposal

Addition of blinatumomab to the complementary list of the EMLc for the treatment of paediatric patients with CD19-positive B-lineage acute lymphoblastic leukaemia (B-ALL) in frontline, relapsed and refractory settings.

Applicant

Resonance, Inc., Memphis, TN, United States of America

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team supported the inclusion of blinatumomab on the EMLc. The team highlighted that inclusion of blinatumomab would provide a valuable opportunity to enhance sustainable and equitable access through initiatives such as the Global Platform for Access to Childhood Cancer Medicines.

EML/EMLc

EMLc

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Powder for concentrate for solution for infusion: 35 micrograms, 38.5 micrograms in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Blinatumomab has not previously been evaluated for inclusion on the EMLc.

The EMLc currently includes the tyrosine kinase inhibitor imatinib for paediatric patients with Philadelphia chromosome positive (Ph+) acute

lymphoblastic leukaemia, and multiple cytotoxic and supportive medicines for unspecified acute lymphoblastic leukaemia.

Public health relevance

According to data from the 2021 Global Burden of Disease study, acute lymphoid leukaemia had a global prevalence of almost 400 000 cases, and an annual incidence of almost 104 000 cases (all ages). In 2021, in people younger than 20 years, the global prevalence and incidence was 387 000 cases and 53 500 cases, respectively (*1*). The number of reported deaths globally due to acute lymphoid leukaemia in 2021 was almost 24 000.

Acute lymphoblastic leukaemia is the most common childhood cancer and is one of the six index cancers of the WHO Global Initiative for Childhood Cancer (*2*). Cure rates are much lower in low- and middle-income countries than in high-income countries, where lack of access to essential medications, barriers to diagnosis and risk stratification, suboptimal supportive care, and inadequate logistical support can lead to excess relapse, death due to toxicity and abandonment of therapy (*3*–*10*).

The number of years of life lost due to the disease is substantial. Estimates of the number of potential years of life lost due to acute lymphoblastic leukaemia range from 66 to 77 in people aged 1–19 years and from 24 to 39 in people older than 20 years (*11*).

Before the availability of blinatumomab, conventional frontline treatment for paediatric patients diagnosed with acute lymphoblastic leukaemia involved systemic, multidrug cytotoxic chemotherapy regimens over multiple years, given in distinct phases: (i) induction (commonly used agents include vincristine, corticosteroids, and asparaginase, with most regimens adding an anthracycline, usually doxorubicin or daunorubicin); (ii) consolidation/intensification (commonly used agents include mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide and cytarabine); and (iii) maintenance (typically low intensity therapy with methotrexate and mercaptopurine) (*12*).

Summary of evidence: benefits

Frontline B-lineage acute lymphoblastic leukaemia

The Children's Oncology Group (COG) AALL1731 study is a phase III trial in which 1440 children (median age 4.3 years, interquartile range (IQR) 2.8 to 6.4 years) with standard-risk B-lineage acute lymphoblastic leukaemia and an average or higher risk of relapse were randomized to receive two cycles of blinatumomab plus chemotherapy ($n = 718$) or chemotherapy alone ($n = 722$) (*13*). At a median follow-up of 2.5 years, the estimated 3-year disease-free survival significantly favoured the blinatumomab plus chemotherapy group (96.0% versus 87.9%; difference in restricted mean survival time, 72 days 95% confidence interval (CI) 36 days to 108 days; $P < 0.001$). Estimated 3-year overall survival was

98.4% and 97.1% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively. The study was terminated early following results from the first interim efficacy analysis.

A prospective, single-arm phase II study evaluated the efficacy and safety of one post-induction course of blinatumomab added to chemotherapy in 30 infants younger than 1 year with newly diagnosed KMT2A-rearranged acute lymphoblastic leukaemia (*14*). Median follow-up was 26.3 months. Two-year disease-free survival with blinatumomab was 81.6% (95% CI 60.8% to 92.0%), compared with that of historical controls with chemotherapy from the Interfant-06 trial (49.4%, 95% CI 42.5% to 56.0%). Corresponding results for overall survival were 93.3% (95% CI 75.9% to 98.3%) with blinatumomab and 65.8% (95% CI 58.9 to 71.8) with chemotherapy.

Relapsed/refractory B-lineage acute lymphoblastic leukaemia

The COG ALL1311 study is a phase III study that compared survival of 255 children, adolescents and young adults aged 1–30 years with low-risk first relapse of B-lineage acute lymphoblastic leukaemia treated with chemotherapy alone or chemotherapy plus blinatumomab (*15*). The primary endpoint was disease-free survival (time from randomization to relapse, second malignancy or death). The secondary endpoint was overall survival (time from randomization to death from any cause). Median follow-up among living patients was 3.5 years. A total of 97 disease-free survival events were reported, 42 in the blinatumomab group and 55 in the chemotherapy group. Among low-risk patients with bone marrow ± extramedullary relapse, the 4-year disease-free survival rates were 53.7% for blinatumomab and 72.7% for chemotherapy (hazard ratio (HR) 0.53, 95% CI 0.30 to 0.95). Four-year overall survival rates were 97.1% for blinatumomab and 84.8% for chemotherapy (HR 0.28, 95% CI 0.08 to 1.02). Among all low-risk patients, the 4-year disease-free survival rates were 49.5% for blinatumomab and 61.2% for chemotherapy (HR 0.76, 95% CI 0.51 to 1.14) and 4-year overall survival rates were 90.4% for blinatumomab and 79.6% for chemotherapy (HR 0.65, 95% CI 0.32 to 1.30).

A 2023 systematic review and meta-analysis of 12 studies (two randomized controlled trials versus chemotherapy and 10 single-arm studies) with 652 participants evaluated the efficacy and safety of blinatumomab in children and adolescents with relapsed/refractory B-lineage acute lymphoblastic leukaemia (*16*). The primary outcomes were complete response, overall survival, event-free survival, minimal residual disease response and allogeneic haematopoietic stem cell transplantation. Results for the randomized controlled trials and single-arm studies were reported separately. Only the single-arm studies reported complete response data. Pooled results showed that 183/336 patients achieved a complete response with a pooled complete response rate of 56% (95% CI 54% to 68%). Overall survival data were reported in the randomized controlled trials

and nine single-arm studies. Pooled data from the trials showed no significant difference between blinatumomab and chemotherapy for 1-year overall survival (odds ratio (OR) 1.51, 95% CI 0.95 to 2.42) but a significant difference favouring blinatumomab for 2-year overall survival (OR 1.97, 95% CI 1.23 to 3.15). All-time overall survival also significantly favoured blinatumomab (OR 1.73, 95% CI 1.24 to 2.41). The pooled overall survival rate from the experimental arm of the randomized controlled trials and the single-arm studies was 43% (95% CI 32% to 54%). Event-free survival data were reported in the randomized controlled trials and five single-arm studies. Pooled data from the trials showed significant differences favouring blinatumomab for 1-year (OR 1.84, 95% CI 1.16 to 2.90), 2-year (OR 2.63, 95% CI 1.58 to 4.39) and all-time event-free survival (OR 2.16, 95% CI 1.54 to 3.03). The pooled event-free survival rate from the experimental arm of the randomized controlled trials and the single-arm studies was 31% (95% CI 21% to 41%). Minimal residual disease response data were reported in all included studies. Pooled data from the randomized controlled trials showed a significant difference favouring blinatumomab (OR 4.71, 95% CI 2.84 to 7.81). The pooled minimal residual disease response rate for blinatumomab from all studies was 51% (95% CI 34% to 68%). Data from the randomized controlled trials reported 82 and 122 patients in the chemotherapy and blinatumomab groups, respectively, received allogeneic haematopoietic stem cell transplantation any time after the first blinatumomab infusion. Pooled data showed a significant difference between treatment groups for allogeneic haematopoietic stem cell transplantation (OR 3.24, 95% CI 1.96 to 5.35) (*16*).

Another 2023 systematic review and meta-analysis of 18 studies (one randomized controlled trial, seven single-arm trials, 10 retrospective studies; 1373 participants) assessed the efficacy and safety of blinatumomab in patients with relapsed/refractory acute lymphoblastic leukaemia, without age restrictions (*17*). The mean age of patients in these studies ranged from 6 months to 58 years. Efficacy outcome measures reported were complete response, minimal residual disease response, overall survival and relapse-free survival. The pooled complete response rate of blinatumomab was 54% (95% CI 44% to 64%; 16 studies, 1249 participants), the pooled minimal residual disease response rate of blinatumomab was 43% (95% CI 34% to 51%; 14 studies, 942 participants), and pooled median overall survival and relapse-free survival of blinatumomab were 8.16 months (95% CI 6.64 to 9.69) and 6.02 months (95% CI 4.63 to 7.41), respectively.

Frontline B-lineage acute lymphoblastic leukaemia – adults

A randomized, phase III trial compared blinatumomab plus chemotherapy versus chemotherapy alone in 224 adults aged 30–70 years with minimal residual disease-negative acute lymphoblastic leukaemia after induction and intensification chemotherapy (*18*). The primary endpoint was overall survival from the time of randomization; relapse-free survival was a secondary endpoint. At a median

follow-up of 42 months, 17 and 40 deaths were reported in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively. The 3-year overall survival was 85% versus 68% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively (HR for death 0.41, 95% CI 0.23 to 0.73). The 3-year relapse-free survival was 80% versus 64% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively (HR for relapse or death 0.53, 95% CI 0.32 to 0.87).

Summary of evidence: harms

In the 2023 systematic review of blinatumomab in relapsed/refractory B-lineage acute lymphoblastic leukaemia in children and adolescents, results of combined data of the randomized controlled trials showed the odds of grade 3 or higher adverse events was significantly reduced in patients randomized to blinatumomab compared with those randomized to chemotherapy (OR 0.31, 95% CI 0.16 to 0.60). The pooled adverse event rate in the experimental arms of the randomized controlled trials and seven single-arm studies was 65% (95% CI 54% to 76%). The most commonly reported adverse events were cytokine release syndrome, neutropenia, death and neurological events. The frequency of cytokine release syndrome, grade 3 or higher neutropenia and death during blinatumomab therapy was 16%, 34% and 24%, respectively (*16*).

In the 2023 systematic review of blinatumomab in relapsed/refractory acute lymphoblastic leukaemia in patients of all ages, analysis of seven prospective studies (743 participants) reported a pooled incidence of grade ≥ 3 adverse events of 80% (95% CI 72% to 88%). The pooled incidence of neurological toxicity grade ≥ 3 was 7% (95% CI 4% to 11%; 12 studies, 885 participants) and the pooled incidence of grade ≥ 3 cytokine release syndrome was 3% (95% CI 2% to 5%; nine studies, 776 participants) (17). Four studies reported haematological toxicity and the pooled incidence was 31% (95% CI 14% to 47%). The most frequently reported haematological toxicities associated with blinatumomab were neutropenia (31%) and anaemia (28%).

A 2022 systematic review and meta-analysis of two phase I/II (97 participants) and two phase III trials (208 participants) evaluated the safety profile of blinatumomab compared with chemotherapy in paediatric patients with B-lineage acute lymphoblastic leukaemia (*19*). Compared to chemotherapy, blinatumomab was associated with a lower risk of febrile neutropenia (risk ratio (RR) 0.13, 95% CI 0.6 to 0.26), infection (RR 0.40, 95% CI 0.29 to 0.56), serious adverse events (RR 0.56, 95% CI 0.32 to 0.99), and adverse events ≥ grade 3 (RR 0.79, 95% CI 0.67 to 0.93). No difference was found between treatment groups in the risk of cytokine release syndrome (RR 8.37, 95% CI 0.27 to 260.97) or seizures (RR 6.43, 95% CI 0.79 to 53.08). Blinatumomab was associated with a higher risk for encephalopathy (RR 8.90, 95% CI 1.08 to 73.29).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of B-lineage acute lymphoblastic leukaemia are not currently available.

Guidelines from the European Society of Medical Oncology, and the National Comprehensive Cancer Network were updated in 2024. Both include recommendations for the use of blinatumomab for people with B-lineage acute lymphoblastic leukaemia regardless of age in the frontline and relapsed/refractory settings (*20*, *21*).

Costs/cost–effectiveness

Available list prices per vial for blinatumomab reported in the application range from 1389 United States dollars (US$) in Mexico to US$ 10 654 in Argentina. Excluding Argentina and the United States (where the reported list price is US$ 5145 per vial), the median price per vial is about US$ 2244.

Although blinatumomab is relatively expensive, it has proven cost-effective in both frontline and relapsed settings because it induces durable remissions and reduces the need for more expensive interventions, such as repeated hospitalizations, intensive chemotherapy, haematopoietic stem cell transplantation and chimeric antigen receptor-T cell therapy (*22*–*27*).

A 2024 study evaluated the cost–effectiveness of blinatumomab versus standard consolidation chemotherapy for treatment of paediatric patients with high-risk, first-relapsed, Philadelphia chromosome-negative B-lineage acute lymphoblastic leukaemia from a Mexican health-care payer perspective (*22*). The study used a decision analytic model to estimate life years and costs over a lifetime horizon and a discount rate of 5%. Analyses were conducted using the medicine acquisition costs for blinatumomab in Mexico in 2023. In the base-case analysis, the incremental cost–effectiveness ratio for blinatumomab versus consolidation chemotherapy was 121 526 Mexican pesos (US$ 6829) per life-year gained. In sensitivity analyses, the incremental cost–effectiveness ratio was most sensitive to the discount rate for costs and outcomes, the percentage of patients undergoing allo-haematopoietic stem cell transplantation, blinatumomab dose and vial sharing. In a probabilistic sensitivity analysis, there was a 99.5% and 87.1% probability of blinatumomab being considered cost-effective at willingness-to-pay thresholds of 600 000 and 200 000 Mexican pesos per life-year gained, respectively. A similar study, with a lifetime horizon and 5% discount rate was conducted from the Brazilian health-system perspective in 2022 (*27*). The base-case incremental cost–effectiveness ratio was 78 873 Brazilian reals per quality-

adjusted life year (US$ 1 = 5.165 reals at the time of the study). Sensitivity analyses found the incremental cost–effectiveness ratio was sensitive to the discount rate, exclusion of blinatumomab waste by vial sharing and change in infusion time. Probabilistic analysis found a 65.7% probability of blinatumomab being cost-effective at a willingness-to-pay threshold of 95 501 Brazilian reals.

Availability

As of October 2024, blinatumomab has regulatory approval in 69 countries. Biosimilars are not currently available. Blinatumomab has been provided in low- and middle-income countries through access programmes in collaboration with St Jude Children's Research Hospital and major academic centres in India, Pakistan and Viet Nam (*28*). The application asserts that access to blinatumomab in low- and middle-income countries is anticipated to improve with support from the WHO Global Platform for Access to Childhood Cancer Medicines.

Other considerations

After developing and validating the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS) for solid tumours, the ESMO-MCBS Working Group has collaborated with the European Hematology Association to develop a version of the scale for haematological malignancies to apply the system in evaluating the magnitude of clinical benefit derived from clinical studies of haematological malignancies (*29*). The application reported that blinatumomab had been evaluated in relapsed/refractory acute lymphoblastic leukaemia in adults based on data from the TOWER study (*30*) and received a score of 5 on the MCBS for haematological malignancies (the highest score for life-extending therapies).

As currently supplied as a lyophilized powder in a single-dose vial for reconstitution, blinatumomab is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump. Administration requires basic infrastructure commonly available in tertiary oncology centres, including infusion pumps, trained medical personnel and central venous access. Special tubing and filters (non-di(2-ethylhexyl) phthalate) are needed for the infusions. These resources are available in most tertiary care centres in low- and middle-income countries (*28*). A phase I/II open-label study investigating the safety, efficacy and pharmacokinetics of subcutaneous blinatumomab for the treatment of acute lymphoblastic leukaemia is ongoing (*31*).

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group supported the inclusion of blinatumomab on the EMLc for the treatment of paediatric patients with B-lineage acute lymphoblastic leukaemia in frontline and relapsed/refractory settings based on a positive benefit–risk profile. The group also suggested an application be sought for the inclusion of blinatumomab on the EML for treatment of adults with B-lineage acute lymphoblastic leukaemia.

Committee recommendations

The Expert Committee considered the disproportionate burden of B-lineage acute lymphoblastic leukaemia in low- and middle-income countries compared to high-income countries, as the number of years of life lost is substantial and cure rates are much lower.

The Committee noted data from randomized clinical trials shows superiority of blinatumomab over chemotherapy in meaningfully improving:

- survival in children, adolescents and adults with relapsed B-lineage acute lymphoblastic leukaemia;
- survival in adults with B-lineage acute lymphoblastic leukaemia in the frontline setting;
- disease-free survival in children with standard risk and higher risk B-lineage acute lymphoblastic leukaemia treated in the frontline setting.

The evidence in adults is more mature, and the effect size in children is similar to that seen in adult patients.

The Committee recognized that blinatumomab is a major advance in therapy for patients with B-lineage acute lymphoblastic leukaemia across all age ranges, and that it should have a considerable impact in low- and middle-income countries by increasing the number of lives saved through treatment. The Committee noted that the application projected that with universal access to blinatumomab in low- and middle-income countries, deaths would fall by 50%.

In response to questions about the maturity of currently available data, the Committee believed that the likelihood of more evidence changing the confidence in the estimates of effect in the relapsed and refractory settings, which are substantial and compelling, was unlikely. The Committee noted that frontline data in adults and children are more recent, with data on adults more mature than the available data on children. However, the Committee was confident that emerging evidence was likely to confirm the benefit of blinatumomab in this setting.

In terms of safety, blinatumomab was shown to be associated with fewer grade ≥ 3 adverse events when compared with chemotherapy; the latter was associated with substantial risks of myelosuppression, infection and secondary malignancies. The Committee highlighted that adverse events specific to blinatumomab, such as cytokine release syndrome and neurotoxicity, and the potential for heightened risk of infections related to induced hypogammaglobulinaemia (which can be prolonged) are important. They therefore require specialist management and may represent a barrier to implementation. The Committee noted the potential need for immunoglobulin treatment to counteract hypogammaglobulinaemia due to B-cell depletion,

and that immunoglobulin is already included on the Model Lists for other indications. The Committee highlighted that training programmes to administer blinatumomab and manage toxicities have been successfully implemented in some in low- and middle-income countries.

Overall, the Committee considered that the balance of benefits to risks of blinatumomab was strongly favourable.

However, the compelling efficacy data notwithstanding, the Committee recognized that a number of barriers existed to implementation including:

- the requirement for intravenous infusion over 4 weeks, necessitating use of central lines and specialized pumps, which are associated with infection risk, additional costs, potential loss of school time in children and the need for supervision by trained staff;
- the currently high acquisition costs for the medicine;
- the cost of supportive care (administration hardware and immunoglobulin).

In considering the feasibility of implementing blinatumomab, the Committee recognized that countries considering including blinatumomab on national EMLs would need to consider their capacity to accommodate requirements for safe administration and management of adverse events. The Committee also noted the requirement of a companion diagnostic test to identify patients with B-lineage acute lymphoblastic leukaemia eligible for treatment.

The Expert Committee noted that toxicity and management of adverse events associated with the existing standard of care for patients with B-ALL also poses feasibility challenges. Treatment has historically relied on intensive multi-agent chemotherapy regimens as salvage therapy, often serving as a bridge to haematopoietic stem cell transplantation or newer immunotherapies. The total duration of treatment is long and varies by phase: induction typically lasts 4 to 6 weeks, followed by consolidation and intensification phases lasting several months. In paediatric protocols, maintenance therapy can extend up to 2-3 years, whereas adults generally receive shorter, more intensive cycles, often prior to transplant or immunotherapy. Adverse effects are frequent and severe, reflecting the intensity of treatment and can include myelosuppression and risk of infection, mucositis, neurotoxicity, cardiotoxicity and hepatotoxicity, depending on the chemotherapeutic regimen used. In children, long-term endocrine or growth effects are also concerns. Adults generally tolerate intensive regimens less well, leading to higher cumulative toxicity and treatment-related mortality.

The Committee noted the current high cost of blinatumomab, and that while it has been determined to be cost-effective in some high-income settings, cost–effectiveness studies in other settings have been variable, depending on patient population and line of therapy.

The Committee appreciated the ongoing efforts of WHO's Global Initiative for Childhood Cancer. The Committee noted that the inclusion of medicines in the Global Platform for Access to Childhood Cancer medicines, which provides cancer medicines for children at no cost to selected countries, is contingent upon their EMLc listing.

Based on these considerations, the Expert Committee recommended the inclusion of blinatumomab on the complementary list of the EML and EMLc for the treatment of children, adolescents and adults with CD19-positive B-lineage acute lymphoblastic leukaemia in frontline and relapsed/refractory settings based on a favourable benefit to risk profile in which clinical cure is a realistic goal.

The Committee considered that national prioritization for use in children and adolescents could be implemented in countries where financial constraints preclude providing blinatumomab for all age groups and where societal values place more weight on life-saving therapies for young people over otherwise equivalent health gains for older people.

The Committee noted that a subcutaneous formulation of blinatumomab is currently being evaluated in clinical trials, with encouraging interim results. The Committee considered that future availability of a subcutaneously administered formulation may significantly reduce the current implementation barriers of central lines and risk of infection. Once available, the Committee advised that it would welcome an application for the subcutaneous formulation for consideration for inclusion on the Model Lists.

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PD-1/PD-L1 immune checkpoint inhibitors – addition – EML

Atezolizumab	**ATC code: L01FF05**
Cemiplimab	**ATC code: L01FF06**
Dostarlimab	**ATC code: L01FF07**
Durvalumab	**ATC code: L01FF03**
Ipilimumab	**ATC code: L01FX04**
Nivolumab	**ATC code: L01FF01**
Pembrolizumab	**ATC code: L01FF02**
Tremelimumab	**ATC code: L01FX20**

Proposal

Addition of programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) immune checkpoint inhibitors atezolizumab, cemiplimab, dostarlimab, durvalumab, ipilimumab and tremelimumab, and extension of the current indications for nivolumab and pembrolizumab for first-line palliative treatment of adults with various locally advanced or metastatic solid tumours on the complementary list of the EML. The proposal covers a total of 25 medicine and indication pairings, as shown in Table 8.

Table 8
Medicine and indication pairings proposed for inclusion on the EML

PD-1/PD-L1 immune checkpoint inhibitor	Indication(s)
Atezolizumab	i. Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%), as monotherapy ii. Hepatocellular carcinoma irrespective of PD-L1 expression, in combination with bevacizumab
Cemiplimab	i. Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%), as monotherapy ii. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with chemotherapy

Table 8 *continued*

PD-1/PD-L1 immune checkpoint inhibitor	Indication(s)
Dostarlimab Durvalumab	i. dMMR/MSI-H endometrial cancer, in combination with chemotherapy i. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with tremelimumab and chemotherapy ii. Hepatocellular carcinoma irrespective of PD-L1 expression, as monotherapy or in combination with tremelimumab iii. Biliary tract cancer irrespective of PD-L1 expression, in combination with chemotherapy
Ipilimumab[a]	i. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with nivolumab and two cycles of chemotherapy ii. Malignant melanoma, in combination with nivolumab iii. Renal cell carcinoma irrespective of PD-L1 expression, in combination nivolumab iv. Oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%, in combination with nivolumab
Nivolumab	i. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with ipilimumab and two cycles of chemotherapy ii. Malignant melanoma, in combination with ipilimumab iii. Renal cell carcinoma irrespective of PD-L1 expression, in combination with ipilimumab iv. Oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%, in combination with ipilimumab v. Oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%, in combination with chemotherapy vi. HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 5, in combination with chemotherapy

Table 8 *continued*

PD-1/PD-L1 immune checkpoint inhibitor	Indication(s)
Pembrolizumab	i. Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%), as monotherapy ii. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with chemotherapy iii. Head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1, in combination with chemotherapy iv. Renal cell carcinoma irrespective of PD-L1 expression, in combination with axitinib or lenvatinib v. Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 10, in combination with chemotherapy vi. HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1, in combination with chemotherapy vii. dMMR/MSI-H colorectal cancer, as monotherapy viii. Triple-negative breast cancer with PD-L1 expression CPS ≥ 10, in combination with chemotherapy ix. Cervical cancer with PD-L1 expression CPS ≥ 1, in combination with chemotherapy
Tremelimumab[a]	i. Oncogenic driver wild-type NSCLC irrespective of PD-L1 expression, in combination with durvalumab and chemotherapy ii. Hepatocellular carcinoma irrespective of PD-L1 expression, in combination with durvalumab.

CPS: combined positive score; dMMR/MSI-H: deficient mismatch repair/microsatellite instability-high; HER2: human epidermal growth factor receptor 2; PD-1: programmed cell death protein 1; PD-L1; programmed death-ligand 1; NSCLC: non-small cell lung cancer; TPS: tumour proportion score.

[a] Only used in combination with other immune-checkpoint inhibitors.

To identify treatment regimens, settings and cancer types best suited for proposed inclusion on the Model Lists, a sequential prioritization framework was defined and followed in which prioritized medicine–indication pairings had to have regulatory approval from the European Medicines Agency (EMA), be used in the palliative first-line setting and have a score of at least 4 on the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) in the non-curative setting.

A search of the EMA's Medicine Finder identified 11 immune checkpoint inhibitors (atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tislelizumab, tremelimumab and relatlimab) for further review. Product information documents were then screened to identify their indicated use, revealing 76 EMA-approved treatment

regimens for 21 cancer indications. Of the identified approvals, 11 were in the curative (neo)adjuvant setting, 44 were in the palliative first-line treatment setting and 19 were for later lines of treatment. Finally, the ESMO-MCBS scorecards for the identified approvals in the palliative first-line setting were evaluated to identify those treatments with substantial benefit (i.e. a score of 4 or 5).

Full details of the prioritization methodology, search strategy and selection criteria can be found in the application document (*1*).

Applicant

WHO Collaborating Center on Evidence Synthesis and Evaluation of Novel Cancer Therapies; Institute of Public Health, Medical Faculty and University Hospital Cologne, University of Cologne, Cologne, Germany

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The team expressed its support for the inclusion of immune checkpoint inhibitors for the prioritized indications identified by the EML cancer expert group, namely:

- Pembrolizumab, atezolizumab and cemiplimab for oncogenic driver wild-type non-small cell lung cancer with PD-L1 expression ≥ 50%, as monotherapy;
- Pembrolizumab for cervical cancer with PD-L1 expression ≥ 1%, in combination with chemotherapy; and
- Pembrolizumab for dMMR/MSI-H colorectal cancer, as monotherapy.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Atezolizumab

Concentrate for solution for infusion: 840 mg/14 mL in vial, 1200 mg/20 mL in vial

Cemiplimab

Concentrate for solution for infusion: 50 mg/mL in 7 mL vial

Dostarlimab

Concentrate for solution for infusion: 50 mg/mL in 10 mL vial

Durvalumab
Concentrate for solution for infusion: 50 mg/mL in 2.4 mL, 10 mL vial

Ipilimumab
Concentrate for solution for infusion: 5 mg/mL in 10 mL vial; 20 mg/mL in 40 mL vial

Nivolumab
Concentrate for solution for infusion: 10 mg/mL in 4 mL, 10 mL, 12 mL, 24 mL vial

Pembrolizumab
Concentrate for solution for infusion: 25 mg/mL in 4 mL vial

Tremelimumab
Concentrate for solution for infusion: 20 mg/mL in 1.25 mL, 15 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Applications for the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the treatment of non-small cell lung cancer were reviewed by the Expert Committee in 2019, 2021 and 2023. On each occasion, inclusion was not recommended.

In 2019, the inclusion of pembrolizumab, nivolumab and atezolizumab was not recommended as the Committee considered that the precise place of these medicines in the treatment of this condition was still evolving (i.e. immunotherapy alone or in combination with chemotherapy). The Committee noted the evidence of efficacy in the treatment of patients with metastatic non-small cell lung cancer with these agents. The Committee observed that the duration of follow-up of the single studies for first-line and second-line immunotherapy in trials for lung cancer was generally shorter than 3 years and considered that data from longer follow-up would better demonstrate the magnitude of benefit. The Committee expressed the hope that by the time of the 2021 Committee meeting, more mature data would be available for metastatic non-small cell lung cancer and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy. Furthermore, the Committee noted that the clinical development of cancer immunotherapy still had some areas of uncertainty about the optimal time for introduction of treatment (first- or second-line), appropriate patient selection (i.e. use of biomarkers) and whether or not the use of immune checkpoint inhibitors in combination with other medicines was superior to

monotherapy. The Committee expressed concern about the potential effect of oncology medicines on health budgets, which could be an impediment to access, and the fact that countries may not be able to list these medicines on their national EMLs because of their high price (*2*).

In 2021, the Committee acknowledged that atezolizumab, durvalumab, nivolumab and pembrolizumab were associated with a relevant median overall survival benefit as first-line treatment, well over the EML threshold of 4 to 6 months, based on evidence from several randomized trials. The Committee also noted that the addition of PD-1/PD-L1 immune checkpoint inhibitors to conventional chemotherapy was associated with modest increases in toxicity that may require specialized management in certain cases. Overall, the Committee considered that these medicines had a favourable benefit-to-harm ratio and acknowledged that they had substantially improved outcomes for the treatment of non-small cell lung cancer in practice. However, their inclusion of was not recommended as the Committee considered that at current prices, these medicines were prohibitively expensive in many settings. The issue of treatment costs and appropriate use of these medicines is further complicated by the need for diagnostic testing to identify patients most likely to benefit from treatment, uncertainties about the optimal duration of treatment, the significant disease burden and the likely large eligible patient population. The Committee considered that the financial implications of listing PD-1/PD-L1 immune checkpoint inhibitors for this indication would result in unsustainable expenditures for many patients and health systems (*3*).

In 2023, the Committee acknowledged possible improvement in quality of life in addition to improved overall survival associated with the use of pembrolizumab compared with platinum-based chemotherapy in patients with advanced or metastatic non-small cell lung cancer expressing high levels of PD-L1. The Committee noted that longer follow-up data were available, with overall survival benefits maintained over a 5-year period. The Committee also noted that atezolizumab and cemiplimab showed similar benefits in prolonging median overall survival compared with platinum-based chemotherapy in the same patient population, although available follow-up data were shorter than for pembrolizumab. For durvalumab as consolidation therapy in locally advanced disease, data also suggested a meaningful benefit; however, the Committee considered that the data were less mature and required further evaluation over time (*4*).

The Committee acknowledged that individual immune checkpoint inhibitors may differ in their efficacy and safety profiles but considered that an overall net benefit could be assumed for the class when compared with platinum-based chemotherapy. The Committee considered that in principle, the availability of several interchangeable immune checkpoint inhibitors could boost competition and favour access. However, the Committee noted that uncertainty remained about the optimal dose and duration of treatment, with ongoing trials investigating use

of lower doses or for a shorter duration. The Committee commended these studies and recommended that such trials be promoted and publicly funded to confirm if lower doses and shorter duration of treatment were indeed associated with non-inferior survival outcomes, similar or lower toxicity and lower costs, and offered a pathway to more affordable and widespread access (*4*).

The Committee noted that prices of immune checkpoint inhibitors have remained prohibitively high in most settings. In the absence of true competition, the Committee remained concerned that this situation would continue to contribute to serious inequities between rich and poor countries and patients, which would result in negligible availability and unaffordable prices for a large proportion of the global population. The Committee also noted the need to select patients that could benefit from treatment based on PD-L1 expression. Affordable access to necessary diagnostics would add an extra burden on countries and listing these medicines without being able to target their use to those patients who would benefit most could lead to additional wasted resources, both public and private (*4*).

The Committee recognized the risk at the country level of listing immune checkpoint inhibitors on the EML, including financial risks based on the current costs of procurement, opportunity costs associated with diverting resources from other diseases, treatments or preventive programmes (e.g. smoking cessation, clean air), and limited feasibility because of barriers to timely access to diagnostics. The Committee considered that the potential financial impact associated with procurement and appropriate use of immune checkpoint inhibitors could be a significant risk to the financial sustainability of health budgets in many low- and middle-income countries. This was especially true if these countries aimed to provide universal treatment coverage, given the high prices of immune checkpoint inhibitors and PD-L1 testing, as well as the high prevalence of non-small cell lung cancer. The Committee recognized that the opportunity costs of providing immune checkpoint inhibitors at current prices for the treatment of patients with non-small cell lung cancer would be substantial for many health systems. The Committee considered that an assessment of various scenarios based on different assumptions on procurement price, capacity to administer and the proportion of patients eligible for treatment would help foster the development of solutions that facilitate access, without bankrupting the health-care budget (*4*).

Nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (*2*).

Public health relevance

Cancer is responsible for nearly one in three premature deaths from noncommunicable disease. It was the leading cause of death in 57 countries worldwide in 2019, and may surpass cardiovascular disease as the leading cause of death globally by the end of this century (*5*).

According to GLOBOCAN, in 2022, about 20 million new cancer cases and almost 10 million cancer deaths were estimated to have occurred. In 2050, the number of new cases is likely to reach about 35 million, an increase of 77%. Since demographic transitions are an important driver of the cancer burden, the absolute increase in cancer cases is predicted to be greatest in countries with high and very high Human Development Indices (HDI), i.e. countries with higher incomes according to the World Bank Classification, and generally older populations. However, relative increases will be highest in medium and low HDI countries, with increases of nearly 100% and 142%, respectively (*6*). This more rapid increase in cancer cases, in conjunction with the disproportionally high cancer death burden in low- and middle-income countries accounting for 70.6% of all cancer deaths (*7*–*8*), projects a substantial worsening of the already existing global inequality in cancer care as a consequence.

Reasons for the high mortality to incidence ratio (70% versus 60%) in low- and middle-income countries include late-stage presentation, barriers to health-care access, and low availability and prohibitively high prices of cancer medicines (*8*–*10*). However, data from high-income countries also show that a substantial proportion of cancers are at an advanced stage at first presentation (*11*). Consequently, a holistic approach is necessary to reduce the global cancer burden effectively, including improved availability, access and affordability of disease-stage appropriate medical oncology treatments and palliative care measures.

Summary of evidence: benefits

Based on a prioritized selection of eight immune checkpoint inhibitors and 12 cancer types, the applicants conducted multiple systematic reviews of randomized controlled trials comparing treatments based on immune checkpoint inhibitors with the established standard of care in the palliative first-line setting. Patient-relevant outcomes of interest were overall survival, progression-free survival, quality of life and higher grade (≥ 3) adverse events.

Biliary tract carcinoma irrespective of PD-L1 expression

One randomized controlled trial of durvalumab plus chemotherapy versus chemotherapy alone was identified that evaluated treatment of unresectable advanced or metastatic biliary tract carcinoma (TOPAZ-1 (*12*, *13*)). Of 685 randomized participants, 341 received durvalumab plus chemotherapy and 344 received chemotherapy. Durvalumab 1500 mg was administered intravenously on day 1, in combination with gemcitabine 1000 mg/m^2 and cisplatin at 25 mg/m^2 body-surface area on days 1 and 8, of eight 21-day cycles.

After a median follow-up of 22.9 months, there was moderate-certainty evidence that durvalumab-containing regimens likely increase overall survival (hazard ratio (HR) for death 0.76, 95% confidence interval (CI) 0.64 to 0.91; one

randomized controlled trial, 685 participants). In absolute terms, 56 versus 47 people per 100, respectively, on durvalumab plus chemotherapy or chemotherapy alone were alive at 1 year, 34 versus 24 people per 100 were alive at 1.5 years, and median overall survival gain was 3.6 months. After a median follow-up of 16.4 months, there was moderate-certainty evidence that durvalumab-containing regimens likely increased progression-free survival (HR for disease progression or death 0.75, 95% CI 0.63 to 0.89; one randomized controlled trial, 685 participants). In absolute terms, 12 versus 6 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab-containing regimens likely have little to no effect on health-related quality of life (mean difference (MD) from baseline 0.88, 95% CI –1.80 to 3.65; one randomized controlled trial, 646 participants).

Cervical cancer with PD-L1 expression ≥ 1%

One randomized controlled trial of pembrolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone was identified that evaluated treatment of metastatic cervical cancer (Keynote-826 (*14*–*16*)). Of 617 participants randomized, 548 had PD-L1 expression of CPS ≥ 1%.

After a median follow-up of 39.1 months, there was high-certainty evidence that pembrolizumab-containing regimens increase overall survival (HR for death 0.60, 95% CI 0.49 to 0.74; one randomized controlled trial, 548 participants). In absolute terms, 57 versus 39 people per 100, respectively, on pembrolizumab plus platinum-based chemotherapy or platinum-based chemotherapy alone were alive at 2 years, 46 versus 27 people per 100 were alive at 3 years and median overall survival gain was 11.0 months. There was high-certainty evidence that pembrolizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.60, 95% CI 0.48 to 0.75; one randomized controlled trial, 548 participants). In absolute terms, 52 versus 34 people per 100 were without disease progression at 1 year. There was high-certainty evidence that pembrolizumab-containing regimens have little to no effect on health-related quality of life (MD from baseline 1.30, 95% CI –3.02 to 5.62; one randomized controlled trial, 519 participants).

Deficient mismatch repair/microsatellite instability-high colorectal cancer

One randomized controlled trial of pembrolizumab monotherapy versus fluoropyrimidine-based chemotherapy was identified that evaluated treatment of deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer irrespective of PD-L1 expression (Keynote-117 (*17*–*19*)). Of 307 randomized participants, 153 received pembrolizumab monotherapy and 154 received the comparator treatment (modified FOLFOX6, modified FOLFOX6 plus bevacizumab, modified FOLFOX6 plus cetuximab, FOLFIRI, FOLFIRI plus bevacizumab, or FOLFIRI plus cetuximab).

After a median follow-up of 44.5 months, there was low-certainty evidence that pembrolizumab may increase overall survival (HR for death 0.74, 95% CI 0.53 to 1.03; one randomized controlled trial, 307 participants). In absolute terms, 60 versus 50 people per 100, respectively, on pembrolizumab monotherapy or fluoropyrimidine-based chemotherapy were alive at 3 years, and median overall survival gain was 12.9 months. There was low-certainty evidence that pembrolizumab may increase progression-free survival (HR for disease progression or death 0.59, 95% CI 0.45 to 0.79; one randomized controlled trial, 307 participants). In absolute terms, 57 versus 39 people per 100 were without disease progression at 3 years. There was low-certainty evidence that pembrolizumab may have little to no effect on health-related quality of life (MD from baseline 8.96, 95% CI 4.24 to 13.69; one randomized controlled trial, 292 participants).

dMMR/MSI-H endometrial cancer

One randomized controlled trial of dostarlimab plus carboplatin and paclitaxel versus carboplatin and paclitaxel was identified that evaluated treatment of dMMR/MSI-H primary advanced or recurrent endometrial cancer (RUBY (*20*–*23*)). Of 494 participants randomized, 118 had dMMR-MSI-H tumours.

After a median follow-up of 36.6 months, there was low-certainty evidence that dostarlimab-containing regimens may result in a large increase in overall survival (HR for death 0.32, 95% CI 0.17 to 0.63; one randomized controlled trial, 118 participants). In absolute terms, 84 versus 57 people per 100, respectively, in the dostarlimab arm or carboplatin arm were alive at 2 years and 78 versus 46 people per 100 were alive at 3 years. Median overall survival was not reached in the dostarlimab arm and was 31.4 months in the chemotherapy arm. An estimated median overall survival gain of 66.7 months was calculated by the applicants, using the HR and baseline risk estimate from the comparator arm. There was moderate-certainty evidence that dostarlimab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.28, 95% CI 0.16 to 0.50; one randomized controlled trial, 118 participants). In absolute terms, 67 versus 24 people per 100 were without disease progression at 1 year. There was low-certainty evidence that dostarlimab-containing regimens may increase health-related quality of life (MD from baseline 9.38, 95% CI 5.45 to 13.31; one randomized controlled trial, 115 participants).

Human epidermal growth factor receptor 2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5

Two randomized controlled trials of pembrolizumab plus chemotherapy versus chemotherapy alone (Keynote-859 (*24*, *25*) and Keynote-062 (*26*–*28*)) and one randomized controlled trial of nivolumab plus chemotherapy versus chemotherapy alone (CheckMate 649 (*29*–*31*)) were identified that evaluated

treatment of human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction adenocarcinoma in patients with PD-L1 expression of CPS ≥ 1 (pembrolizumab) or CPS ≥ 5 (nivolumab).

After a median follow-up of 30.2 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival compared with chemotherapy (HR for death 0.78, 95% CI 0.68 to 0.89; two randomized controlled trials, 1742 participants). In absolute terms, 26 versus 18 people per 100, respectively, on pembrolizumab plus chemotherapy or chemotherapy alone were alive at 2 years, and median overall survival gain was 3.2 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.77, 95% CI 0.66 to 0.89; two randomized controlled trials, 1874 participants). In absolute terms, 14 versus 8 people per 100 were without disease progression at 2 years. There was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on health-related quality of life (MD from baseline 1.25, 95% CI –1.07 to 3.58; one randomized controlled trial, 1542 participants).

After a median follow-up of 47.4 months, there was moderate-certainty evidence that nivolumab-containing regimens likely increase overall survival compared with chemotherapy (HR for death 0.70, 95% CI 0.61 to 0.81; one randomized controlled trial, 955 participants). In absolute terms, 31 versus 19 people per 100, respectively, on nivolumab-containing regimens or chemotherapy were alive at 2 years and median overall survival gain was 4.8 months. There was low-certainty evidence that nivolumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.70, 95% CI 0.60 to 0.81; one randomized controlled trial, 955 participants). In absolute terms, 21 versus 11 people per 100 were without disease progression at 2 years. There was moderate-certainty evidence that nivolumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline 6.42, 95% CI 0.67 to 12.17; one randomized controlled trial, 797 participants).

Head and neck squamous cell carcinoma with PD-L1 expression combined positive score ≥ 1

One randomized controlled trial of pembrolizumab as monotherapy or in combination with platinum-based chemotherapy versus platinum-based chemotherapy and cetuximab was identified that evaluated treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (Keynote-048 (*32*–*35*)). Of 882 randomized participants, 301 received pembrolizumab monotherapy, 281 received pembrolizumab-based chemotherapy and 300 received the comparator treatment. PD-L1 expression CPS ≥ 1 was equally distributed in intervention and comparator arms and was found in about 85% of participants. Data extracted compared pembrolizumab-based chemotherapy versus cetuximab-based chemotherapy only, as this was the only combination that satisfied the inclusion criteria applied by the applicants.

After a median follow up of 45 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase overall survival (HR for death 0.64, 95% CI 0.53 to 0.78; one randomized controlled trial, 477 participants). In absolute terms, 32 versus 17 people per 100, respectively, on pembrolizumab-based chemotherapy or cetuximab-based chemotherapy were alive at 2 years, 21 versus 9 people per 100 were alive at 3 years and median overall survival gain was 6.0 months. After a median follow-up of 11.9 months, there was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on progression-free survival (HR for disease progression or death 0.82, 95% CI 0.67 to 1.00; one randomized controlled trial, 477 participants). In absolute terms, 16 versus 11 people per 100 were without disease progression at year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in health-related quality of life (MD from baseline 0.40, 95% CI -3.80 to 4.60; one randomized controlled trial, 527 participants).

Hepatocellular carcinoma irrespective of PD-L1 expression

Two randomized controlled trials of atezolizumab plus bevacizumab versus sorafenib (IMbrave 150 (*36*–*38*)), and durvalumab as monotherapy or in combination with chemotherapy versus sorafenib (HIMALAYA (*39*–*41*)) were identified that evaluated treatment of hepatocellular carcinoma.

For the comparison of atezolizumab-containing regimens versus sorafenib, after a median follow-up of 15.6 months, there was moderate-certainty evidence that atezolizumab-containing regimens likely increase overall survival (HR for death 0.66, 95% CI 0.52 to 0.85; one randomized controlled trial, 501 participants). In absolute terms, 55 versus 40 people per 100, respectively, on atezolizumab-containing regimens or sorafenib were alive at 1.5 years and median overall survival gain was 6.9 months. There was moderate-certainty evidence that atezolizumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.65, 95% CI 0.53 to 0.81; one randomized controlled trial, 501 participants). In absolute terms, 36 versus 21 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that atezolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline 2.54, 95% CI –1.31 to 6.39; one randomized controlled trial, 481 participants).

For the comparison of durvalumab monotherapy versus sorafenib, after a median follow-up of 47.9 months, there was low-certainty evidence that durvalumab may increase overall survival (HR for death 0.86, 95% CI 0.74 to 1.01; one randomized controlled trial, 778 participants). In absolute terms, 38 versus 33 people per 100, respectively, on durvalumab monotherapy or sorafenib were alive at 2 years, 20 versus 15 people per 100 were alive at 4 years and median overall

survival gain was 2.3 months. After a median follow-up of 32.4 months, there was moderate-certainty evidence that durvalumab monotherapy likely results in little to no difference in progression-free survival (HR for disease progression or death 1.02, 95% CI 0.88 to 1.19; one randomized controlled trial, 778 participants). In absolute terms, 32 versus 33 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab monotherapy likely has little to no effect on health-related quality of life (MD from baseline 4.30, 95% CI 0.41 to 8.19; one randomized controlled trial, 778 participants).

For the comparison of durvalumab plus tremelimumab versus sorafenib, after a median follow-up of 48.2 months, there was moderate-certainty evidence that durvalumab plus tremelimumab likely increases overall survival (HR for death 0.78, 95% CI 0.67 to 0.92, one randomized controlled trial, 782 participants). In absolute terms, 42 versus 33 people per 100, respectively, on durvalumab plus tremelimumab or sorafenib were alive at 2 years, 23 versus 15 people per 100 were alive at 4 years and median overall survival gain was 3.9 months. After a median follow-up of 32.7 months, there was low-certainty evidence that durvalumab plus tremelimumab may increase progression-free survival (HR for disease progression or death 0.90, 95% CI 0.77 to 1.05; one randomized controlled trial, 782 participants). In absolute terms, 37 versus 33 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that durvalumab plus tremelimumab likely has little to no effect on health-related quality of life (MD from baseline –0.35, 95% CI –4.21 to 3.51; one randomized controlled trial, 782 participants).

Malignant melanoma

Five randomized controlled trials of ipilimumab plus nivolumab for the treatment of malignant melanoma were identified. Three randomized controlled trials included patients irrespective of PD-L1 expression and *BRAF* V600 mutation status (ABC (*42*, *43*), CheckMate 067 (*44*, *45*) and CheckMate 069 (*46*, *47*)), and two randomized controlled trials included patients irrespective of PD-L1 mutation status and with *BRAF* V600-mutant disease (DREAMseq/EA6134 (*48*, *49*) and SECOMBIT (*50*)). A total of 1537 participants were randomized: 639 to ipilimumab plus nivolumab and 898 to one of the control regimens. Among randomized participants, 346 receiving ipilimumab plus nivolumab and 422 receiving a control regimen had a *BRAF* V600 mutation. A vast majority of participants included in this review did not have brain metastases. Ipilimumab was administered at a dose of 3 mg/kg and nivolumab at a dose of 1 mg/kg on day 1 of four 3-week cycles. Subsequently, patients received nivolumab 3 mg/kg on day 1 of 2-week cycles. Treatment continued for: up to 2 years of nivolumab administration; until disease progression; until development of unacceptable toxicity; or on withdrawal of consent. Ipilimumab plus nivolumab

was compared with: ipilimumab monotherapy 3 mg/kg on day 1 of four 3-week cycles (CheckMate 067 and CheckMate 069); nivolumab monotherapy 3 mg/kg on day 1 of 2-week cycles (ABC and CheckMate 067); BRAF/MEK inhibitor combination dabrafenib 150 mg twice daily and trametinib 2 mg once daily (DREAMseq); and BRAF/MEK inhibitor combination encorafenib 450 mg once daily and binimetinib 45 mg twice daily (SECOMBIT).

For the comparison of ipilimumab plus nivolumab versus immune-checkpoint inhibitor monotherapy, after a median follow-up of 34.6 months, there was moderate-certainty evidence that ipilimumab plus nivolumab likely increases overall survival (HR for death 0.68, 95% CI 0.50 to 0.93; three randomized controlled trials, 1133 participants). In absolute terms, 64 versus 52 people per 100, respectively, on ipilimumab plus nivolumab or immune-checkpoint inhibitor monotherapy were alive at 2 years, 49 versus 35 people per 100 were alive at 5 years and median overall survival gain was 12.8 months. After a median follow-up of 35.7 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase progression-free survival (HR for disease progression or death 0.50, 95% CI 0.31 to 0.82; two randomized controlled trials, 1087 participants). In absolute terms, 49 versus 24 people per 100 were without disease progression at 2 years. There was moderate-certainty evidence that ipilimumab plus nivolumab likely results in little to no difference in health-related quality of life (MD from baseline -1.08, 95% CI –3.44 to 1.28; one randomized controlled trial, 758 participants).

For the comparison of ipilimumab plus nivolumab versus BRAF/MEK inhibitors for BRAF V600-mutant disease, after a median follow-up of 32.2 months, the evidence was very uncertain about the effect of ipilimumab plus nivolumab on overall survival (HR for death 0.73, 95% CI 0.42 to 1.27; one randomized controlled trial, 138 participants). In absolute terms, 73 versus 65 people per 100, respectively, on ipilimumab plus nivolumab or BRAF/MEK inhibitors were alive at 2 years and 64 versus 54 people per 100 were alive at 5 years. Median overall survival was not reached in either group. The evidence was very uncertain about the effect of ipilimumab plus nivolumab on progression-free survival. Pooled 2-year progression-free survival rates were 40.1% versus 23.9% (two randomized controlled trials, 403 participants). Health-related quality of life was not reported.

Oncogenic driver wild-type non-small cell lung cancer with high PD-L1 expression (tumour proportion score ≥ 50%)

Five randomized controlled trials of atezolizumab (IMpower 110 (*51*, *52*) and IPSOS (*53*)), cemiplimab (EMPOWER-Lung1 (*54*–*56*)) and pembrolizumab (Keynote-024 (*57*–*59*) and, Keynote-042 (*60*, *61*)) were identified that evaluated treatment, as monotherapy, of non-small cell lung cancer without oncogenic driver mutations (*EGFR*, *ALK*) and PD-L1 expression ≥ 50%. All studies were global, multicentre, unblinded phase III randomized controlled trials comparing

immune-checkpoint inhibitor monotherapy with the established standard of care for non-small cell lung cancer, with the exception of IPSOS, which was conducted in a patient setting where no clearly established standard treatment exists (patients ineligible for platinum-based chemotherapy). Patients with squamous cell or non-squamous cell tumours that were negative for *EGFR* or *ALK* driver mutations were eligible for inclusion.

After median follow-up of 60.7 months, there was moderate-certainty evidence that pembrolizumab monotherapy likely increases overall survival compared with platinum-based doublet chemotherapy (hazard ratio (HR) for death 0.66, 95% CI 0.57 to 0.76; two randomized controlled trials, 904 participants). In absolute terms, 45 versus 30 people per 100, respectively, on pembrolizumab monotherapy or platinum-based doublet chemotherapy were alive at 2 years and 22 versus 10 people per 100 were alive at 5 years and median overall survival gain was 6.3 months. There was low-certainty evidence that pembrolizumab monotherapy may increase progression-free survival (HR for disease progression or death 0.66, 95% CI 0.39 to 1.12; two randomized controlled trials, 904 participants). In absolute terms, 35 versus 21 people per 100 were without disease progression at 1 year. There was low-certainty evidence that pembrolizumab monotherapy may increase health-related quality of life (MD from baseline 7.85, 95% CI 2.51 to 13.19; one randomized controlled trial, 297 participants).

After median follow-up of 35.6 months, there was low-certainty evidence that atezolizumab monotherapy may increase overall survival compared with chemotherapy (HR for death 0.79, 95% CI 0.54 to 1.09; two randomized controlled trials, 280 participants). In absolute terms, 39 versus 30 people per 100, respectively, on atezolizumab monotherapy or chemotherapy were alive at 2 years and median overall survival gain was 3.7 months. There was low-certainty evidence that atezolizumab monotherapy may increase progression-free survival (HR for disease progression or death 0.63, 95% CI 0.48 to 0.84; two randomized controlled trials, 280 participants). In absolute terms, 34 versus 18 people per 100 were without disease progression at 1 year. Health-related quality of life for atezolizumab was not reported.

After median follow-up of 35.0 months, there was moderate-certainty evidence that cemiplimab monotherapy likely increases overall survival compared with platinum-based doublet chemotherapy (HR for death 0.63, 95% CI 0.52 to 0.77; one randomized controlled trial, 712 participants). In absolute terms, 50 versus 34 people per 100, respectively on cemiplimab monotherapy or platinum-based doublet chemotherapy were alive at 2 years, 40 versus 23 people per 100 were alive at 3 years and median overall survival gain was 8.0 months. There was moderate-certainty evidence that cemiplimab monotherapy likely increases progression-free survival (HR for disease progression or death 0.56, 95% CI 0.47 to 0.67; one randomized controlled trial, 712 participants). In absolute terms,

24 versus 8 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that cemiplimab monotherapy likely results in little to no difference in health-related quality of life (MD from baseline 5.03 (95% CI 2.11 to 7.96; one randomized controlled trial, 563 participants).

Oncogenic driver wild-type non-small cell lung cancer irrespective of PD-L1 expression

Eight randomized controlled trials of (i) pembrolizumab plus platinum-based chemotherapy (Keynote-021 (62, 63), Keynote-189 (64–66) and Keynote-407 (67–69)); (ii) cemiplimab plus platinum-based chemotherapy (EMPOWER-Lung3 (70–72)); (iii) ipilimumab plus nivolumab plus chemotherapy (CheckMate 9LA (73–75)); (iv) durvalumab plus tremelimumab plus chemotherapy (POSEIDON (76, 77)); and (v) tislelizumab plus platinum-based chemotherapy (RATIONALE-307 (78–80) and RATIONALE-304 (81–84)), each versus platinum-based doublet chemotherapy, were identified that evaluated treatment of non-small cell lung cancer without oncogenic driver mutations (EGFR, ALK) irrespective of PD-L1 expression. All studies were global multicentre phase III randomized controlled trials, except for Keynote-021, which was a phase I/II randomized controlled trial. Keynote-189, Keynote-407 and EMPOWER-Lung3 were double-blinded, comparing immune-checkpoint inhibitor-based regimens with an active chemotherapeutic backbone and placebo. Keynote-021, CheckMate 9LA, POSEIDON and CheckMate 9LA were unblinded. All studies followed the same basic structure of comparing the addition of an immune-checkpoint inhibitor or immune-checkpoint inhibitor-doublet to platinum-based chemotherapy with platinum-based chemotherapy alone.

After a median follow-up of 59.8 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.66, 95% CI 0.58 to 0.74; three randomized controlled trials, 1298 participants). In absolute terms, 48 versus 33 people per 100, respectively, on pembrolizumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 22 versus 10 people per 100 were alive at 5 years and median overall survival gain was 6.3 months. There was high-certainty evidence that pembrolizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.55, 95% CI 0.48 to 0.64; three randomized controlled trials, 1298 participants). In absolute terms, 43 versus 21 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens may result in little to no difference in health-related quality of life (MD from baseline 5.00, 95% CI 2.13 to 7.87; two one randomized controlled trials, 1156 participants).

After a median follow-up of 28.4 months, there was moderate-certainty evidence that cemiplimab-containing regimens likely increase overall survival

compared with platinum-based doublet chemotherapy (HR for death 0.65, 95% CI 0.51 to 0.82; one randomized controlled trial, 466 participants). In absolute terms, 43 versus 27 people per 100, respectively, on cemiplimab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years and median overall survival gain was 6.9 months. There was high-certainty evidence that cemiplimab-containing regimens increase progression-free survival (HR for disease progression or death 0.55, 95% CI 0.44 to 0.68; one randomized controlled trial, 466 participants). In absolute terms, 37 versus 16 people per 100 were without disease progression at 1 year. There was high-certainty evidence that cemiplimab-containing regimens do not increase health-related quality of life (MD from baseline 0.61, 95% CI –2.23 to 3.45; one randomized controlled trial, 466 participants).

After a median follow-up of 54.5 months, there was low-certainty evidence that ipilimumab plus nivolumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.74, 95% CI 0.63 to 0.87; one randomized controlled trial, 719 participants). In absolute terms, 37 versus 26 people per 100, respectively, on ipilimumab plus nivolumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 20 versus 11 people per 100 were alive at 5 years and median overall survival gain was 3.9 months. There was moderate-certainty evidence that ipilimumab plus nivolumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.70, 95% CI 0.59 to 0.83; one randomized controlled trial, 719 participants). In absolute terms, 31 versus 19 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that ipilimumab plus nivolumab-containing regimens have little to no effect on health-related quality of life (MD from baseline 4.70, 95% CI –3.26 to 12.66; one randomized controlled trial, 646 participants).

After a median follow-up of 63.4 months, there was low-certainty evidence that durvalumab plus tremelimumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.77, 95% CI 0.65 to 0.92; one randomized controlled trial, 675 participants). In absolute terms, 31 versus 22 people per 100, respectively, on durvalumab plus tremelimumab-containing regimens or platinum-based doublet chemotherapy were alive at 2 years, 13 versus 7 people per 100 were alive at 5 years and median overall survival gain was 3.5 months. After a median follow-up of 10.3 months, there was moderate-certainty evidence that durvalumab plus tremelimumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.72, 95% CI 0.60 to 0.86; one randomized controlled trial, 675 participants). In absolute terms, 23 versus 13 people per 100 were without disease progression at 1 year. Health-related quality of life was not reported.

After a median follow-up of 16.4 months, there was low-certainty evidence that tislelizumab-containing regimens may increase overall survival compared with platinum-based doublet chemotherapy (HR for death 0.80, 95% CI 0.62 to 1.02; two randomized controlled trials, 694 participants). In absolute terms, 75 versus 69 people per 100, respectively, on tislelizumab-containing regimens or platinum-based doublet chemotherapy were alive at 1 year and median overall survival gain was 4.5 months. There was high-certainty evidence that tislelizumab-containing regimens increase progression-free survival (HR for disease progression or death 0.51, 95% CI 0.40 to 0.66; two randomized controlled trials, 694 participants). In absolute terms, 37 versus 14 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that tislelizumab-containing regimens likely result in little to no difference in health-related quality of life (MD from baseline 3.70, 95% CI −0.06 to 7.46; two randomized controlled trials, 687 participants).

Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10

One randomized controlled trial of pembrolizumab plus chemotherapy versus chemotherapy alone (Keynote-590 (*85*–*87*)) and one of nivolumab plus chemotherapy or ipilimumab plus nivolumab versus chemotherapy alone (CheckMate 648 (*88*, *89*)) were identified that evaluated treatment of advanced oesophageal squamous cell carcinoma. The review included only the subgroup of participants in Keynote-590 with PD-L1 expression CPS ≥ 10, and the subgroup of participants in CheckMate 648 with PD-L1 expression on tumour cells (TC) ≥ 1%, in line with the prioritization framework.

After a median follow-up of 22.6 months, there was low-certainty evidence that pembrolizumab plus chemotherapy may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression CPS ≥ 10 (HR for death 0.57, 95% CI 0.43 to 0.75; one randomized controlled trial, 286 participants). In absolute terms, 34 versus 15 people per 100, respectively, on pembrolizumab plus chemotherapy or platinum-based chemotherapy were alive at 2 years and median overall survival gain was 6.6 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.53, 95% CI 0.40 to 0.60; one randomized controlled trial, 286 participants). In absolute terms, 17 versus 4 people per 100 were without disease progression at 2 years. There was low-certainty evidence that pembrolizumab-containing regimens may have little to no effect on health-related quality of life (MD from baseline -1.95, 95% CI −7.72 to 3.82; one randomized controlled trial, 274 participants).

After a median follow-up of 39.5 months, there was low-certainty evidence that nivolumab plus chemotherapy may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression TC ≥ 1%

(HR for death 0.59, 95% CI 0.46 to 0.76; one randomized controlled trial, 315 participants). In absolute terms, 29 versus 12 people per 100, respectively, on nivolumab plus chemotherapy or platinum-based chemotherapy were alive at 2 years, 26 versus 10 people per 100 were alive at 3 years, and median overall survival gain was 6.3 months. There was moderate-certainty evidence that nivolumab plus chemotherapy likely increases progression-free survival (HR for disease progression or death 0.67, 95% CI 0.51 to 0.89; one randomized controlled trial, 315 participants). In absolute terms, 21 versus 10 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that nivolumab plus chemotherapy likely has little to no effect on health-related quality of life (MD from baseline 3.44, 95%–CI –0.03 to 6.91; one randomized controlled trial, 522 participants).

After a median follow up of 39.7 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase overall survival compared with platinum-based chemotherapy in patients with PD-L1 expression TC ≥ 1% (HR for death 0.62, 95% CI 0.48 to 0.80; one randomized controlled trial, 315 participants). In absolute terms, 27 versus 12 people per 100, respectively, on ipilimumab plus nivolumab or platinum-based chemotherapy were alive at 2 years, 24 versus 10 people per 100 were alive at 3 years and median overall survival gain was 5.6 months. There was low-certainty evidence that ipilimumab plus nivolumab may have little to no effect on progression-free survival (HR for disease progression or death 1.04, 95% CI 0.79 to 1.36; one randomized controlled trial, 315 participants). In absolute terms, 9 versus 10 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that ipilimumab plus nivolumab likely has little to no effect on health-related quality of life (MD from baseline 1.91, 95% CI -1.70 to 5.51; one randomized controlled trial, 529 participants).

Renal cell carcinoma irrespective of PD-L1 expression

Two randomized controlled trials of ipilimumab plus nivolumab versus sunitinib (BOINIKK (*90*–*92*), CheckMate 214 (*93*–*95*)) and two randomized controlled trials of pembrolizumab plus axitinib or lenvatinib versus sunitinib (Keynote-426 (*96*–*100*), CLEAR (*101*–*104*)) were identified that evaluated treatment of renal cell carcinoma.

For the comparison of ipilimumab plus nivolumab versus sunitinib, after a median follow-up of 92.6 months, there was low-certainty evidence that ipilimumab plus nivolumab may increase overall survival (HR for death 0.72, 95% CI 0.62 to 0.84; two randomized controlled trials, 1178 participants). In absolute terms, 69 versus 60 people per 100, respectively, on ipilimumab plus nivolumab or sunitinib were alive at 2 years, 48 versus 36 people per 100 were alive at 5 years and median overall survival gain was 13 months. There was

low-certainty evidence that ipilimumab plus nivolumab may result in little to no difference in progression-free survival (HR for disease progression or death 0.96, 95% CI 0.66 to 1.40; two randomized controlled trials, 1169 participants). In absolute terms, 45 versus 43 people per 100 were without disease progression at 1 year. There was low-certainty evidence that ipilimumab plus nivolumab may increase health-related quality of life (MD from baseline 6.28, 95% CI 2.60 to 9.96; one randomized controlled trial, 923 participants).

For the comparison of pembrolizumab plus axitinib or lenvatinib versus sunitinib, after a median follow-up of 59.2 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival (HR for death 0.83, 95% CI 0.72 to 0.94; two randomized controlled trials, 1573 participants). In absolute terms, 72 versus 67 people per 100, respectively, on pembrolizumab-containing regimens or sunitinib were alive at 2 years, 44 versus 37 people per 100 were alive at 5 years and median overall survival gain was 9.6 months. After a median follow-up of 37.1 months, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase progression-free survival (HR for disease progression or death 0.54, 95% CI 0.33 to 0.86; two randomized controlled trials, 1573 participants). In absolute terms, 64 versus 43 people per 100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline −0.34, 95% CI −2.78 to 2.10; two randomized controlled trials, 1546 participants).

Triple-negative breast cancer with PD-L1 expression ≥ 10%

One randomized controlled trial of pembrolizumab plus chemotherapy versus chemotherapy was identified that evaluated treatment of advanced/metastatic triple-negative breast cancer (Keynote-355 (*105*–*107*)). Of 847 participants randomized, 323 had PD-L1 CPS ≥ 10% and among those with PD-L1 CPS ≥ 10, 220 received pembrolizumab plus chemotherapy and 103 received chemotherapy. Chemotherapy was the investigator's choice of nab-paclitaxel, paclitaxel or gemcitabine plus carboplatin.

After a median follow-up of 44.1 months, there was low-certainty evidence that pembrolizumab-containing regimens may increase overall survival compared with chemotherapy alone (HR for death 0.73, 95% CI 0.55 to 0.95; one randomized controlled trial, 323 participants). In absolute terms, 45 versus 34 people per 100, respectively, on pembrolizumab regimens or chemotherapy were alive at 2 years, 34 versus 23 people per 100 were alive at 3 years and median overall survival gain was 6.0 months. There was low-certainty evidence that pembrolizumab-containing regimens may increase progression-free survival (HR for disease progression or death 0.66, 95% CI 0.50 to 0.88; one randomized controlled trial, 323 participants). In absolute terms, 38 versus 23 people per

100 were without disease progression at 1 year. There was moderate-certainty evidence that pembrolizumab-containing regimens likely have little to no effect on health-related quality of life (MD from baseline –1.80, 95% CI –7.33 to 3.73; one randomized controlled trial, 317 participants).

Summary of evidence: harms

Biliary tract carcinoma irrespective of PD-L1 expression

There was high-certainty evidence that durvalumab-containing regimens result in little to no difference in grade ≥ 3 adverse events (risk ratio (RR) 0.98, 95% CI 0.91 to 1.06; one randomized controlled trial, 680 participants).

Cervical cancer with PD-L1 expression ≥ 1%

There was moderate-certainty evidence that pembrolizumab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.09, 95% CI 1.01 to 1.19; one randomized controlled trial, 616 participants).

dMMR/MSI-H colorectal cancer

There was low-certainty evidence that pembrolizumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.72, 95% CI 0.61 to 0.85; one randomized controlled trial, 296 participants).

dMMR/MSI-H endometrial cancer

There was low-certainty evidence that dostarlimab-containing regimens may increase grade ≥ 3 adverse events (RR 1.20, 95% CI 1.06 to 1.36; one randomized controlled trial, 487 participants).

HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5

There was low-certainty evidence that pembrolizumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.11, 95% CI 1.01 to 1.23; two randomized controlled trials, 2066 participants).

There was low-certainty evidence that nivolumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.35, 95% CI 1.23 to 1.49; one randomized controlled trial, 1549 participants).

Head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1

There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.02, 95% CI 0.95 to 1.10; one randomized controlled trial, 563 participants).

Hepatocellular carcinoma irrespective of PD-L1 expression

For the comparison of atezolizumab plus bevacizumab versus sorafenib, there was very-low-certainty evidence that atezolizumab plus bevacizumab may result in little to no difference in grade ≥ 3 adverse events (RR 1.11, 95% CI 0.97 to 1.28; one randomized controlled trial, 485 participants).

For the comparison of durvalumab monotherapy versus sorafenib, there was low-certainty evidence that durvalumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.73, 95% CI 0.64 to 0.85; one randomized controlled trial, 762 participants).

For the comparison of durvalumab plus tremelimumab versus sorafenib, there was moderate-certainty evidence that durvalumab plus tremelimumab likely results in little to no difference in grade ≥ 3 adverse events (RR 0.98, 95% CI 0.87 to 1.10; one randomized controlled trial, 762 participants).

Malignant melanoma

For the comparison of ipilimumab plus nivolumab versus immune-checkpoint inhibitor monotherapy, there was high-certainty evidence that ipilimumab plus nivolumab increases grade ≥ 3 adverse events (RR 2.37, 95% CI 2.03 to 2.77; three randomized controlled trials, 1137 participants).

For the comparison of ipilimumab plus nivolumab versus BRAK/MEK inhibitors for BRAF V600-mutant disease, there was low-certainty evidence that ipilimumab plus nivolumab may increase grade ≥ 3 adverse events (RR 1.26, 95% CI 0.94 to 1.69; two randomized controlled trials, 394 participants).

Oncogenic driver wild-type non-small cell lung cancer with high PD-L1 expression (TPS ≥ 50%)

There was moderate-certainty evidence that pembrolizumab monotherapy likely reduces grade ≥ 3 adverse events (risk ratio (RR) 0.49, 95% CI 0.37 to 0.66; two randomized controlled trials, 1555 participants).

There was low-certainty evidence that atezolizumab monotherapy may reduce grade ≥ 3 adverse events (RR 0.81, 95% CI 0.54 to 1.22; two randomized controlled trials, 996 participants).

There was low-certainty evidence that cemiplimab monotherapy may reduce grade ≥ 3 adverse events (RR 0.89, 95% CI 0.76 to 1.03; one randomized controlled trial, 699 participants).

Oncogenic driver wild-type non-small cell lung cancer irrespective of PD-L1 expression

There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.08, 95% CI 1.00 to 1.16; three randomized controlled trials, 1286 participants).

There was moderate-certainty evidence that cemiplimab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.39, 95% CI 1.06 to 1.81; one randomized controlled trial, 465 participants).

There was low-certainty evidence that ipilimumab plus nivolumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.21, 95% CI 1.05 to 1.40; one randomized controlled trial, 707 participants).

There was moderate-certainty evidence that durvalumab plus tremelimumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.05, 95% CI 0.92 to 1.21; one randomized controlled trial, 664 participants).

There was very-low-certainty evidence that tislelizumab-containing regimens may increase grade ≥ 3 adverse events (RR 1.11, 95% CI 0.93 to 1.34; two randomized controlled trials, 687 participants).

Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10

There was low-certainty evidence that pembrolizumab plus chemotherapy may result in little to no difference in grade ≥ 3 adverse events (RR 1.03, 95% CI 0.97 to 1.10; one randomized controlled trial, 740 participants).

There was low-certainty evidence that nivolumab plus chemotherapy may increase grade ≥ 3 adverse events (RR 1.33, 95% CI 1.11 to 1.61; one randomized controlled trial, 614 participants).

There was low-certainty evidence that ipilimumab plus nivolumab may reduce grade ≥ 3 adverse events (RR 0.91, 95% CI 0.73 to 1.13; one randomized controlled trial, 626 participants).

Renal cell carcinoma irrespective of PD-L1 expression

For the comparison of ipilimumab plus nivolumab versus sunitinib, there was low-certainty evidence that ipilimumab plus nivolumab may reduce grade ≥ 3 adverse events (RR 0.82, 95% CI 0.64 to 1.04; two randomized controlled trials, 1223 participants).

For the comparison of pembrolizumab plus axitinib or lenvatinib versus sunitinib, there was moderate-certainty evidence that pembrolizumab-containing regimens likely increase grade ≥ 3 adverse events (RR 1.11, 95% CI 1.04 to 1.18; two randomized controlled trials, 1546 participants).

Triple-negative breast cancer with PD-L1 expression ≥ 10%

There was moderate-certainty evidence that pembrolizumab-containing regimens likely result in little to no difference in grade ≥ 3 adverse events (RR 1.06, 95% CI 0.97 to 1.15; one randomized controlled trial, 843 participants).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of solid tumours are not currently available.

Costs/cost–effectiveness

No evidence was presented in the application on costs or cost–effectiveness of the various interventions.

A separate report, prepared by Arianna Schouten, Knowledge Ecology International, presented an analysis of financial implications of pembrolizumab and nivolumab and the potential impact of their inclusion on the EML (*108*).

The report highlighted that immune checkpoint inhibitors are still prohibitively expensive, especially in low- and middle-income countries. The report explored the financial and policy landscape surrounding these medicines and discussed strategic pathways that can support improved affordability and access.

Key patents for pembrolizumab and nivolumab are set to expire between 2028 and 2033, and subsequent market entry of biosimilars presents an important opportunity to reduce costs. Pembrolizumab has broader indications and a stronger biosimilar pipeline, and so is expected to face greater pricing pressure, potentially leading to price reductions of up to 60%. Nivolumab, with fewer indications and a less competitive pipeline, may see more moderate reductions of between 25% and 40%.

However, biosimilar entry may be delayed by evergreening strategies employed by originator companies. These include the development of subcutaneous formulations (*109*), which can secure new patents and extend market exclusivity beyond the original expiry dates – potentially up to 2039 in the case of pembrolizumab. These strategies affect competition and may hinder timely access to biosimilars, especially in high-revenue markets. Policy-makers must weigh the trade-offs between supporting biosimilar intravenous formulations and newer subcutaneous versions that may prolong exclusivity.

The report highlighted that despite sharing many common treatment indications and potentially acting as within-class treatment alternatives, there has been limited within-class market competition, with spending on individual immune checkpoint inhibitors remaining relatively stable over time. Factors identified that may contribute to the lack of within-class market competition include market segmentation based on indication, the role of biomarkers and limited direct head-to-head comparative studies of individual immune checkpoint inhibitors.

Current pricing levels often exceed national cost–effectiveness thresholds and may still exceed these thresholds despite potential price reductions following biosimilar entry. Thus, the report emphasizes the importance of a multifaceted strategy to address price and competition and improve affordability and access.

Additional strategies include a supportive policy environment favouring the uptake of biosimilars, pooled procurement mechanisms to make use of collective bargaining and reduce prices, and voluntary and compulsory licensing to overcome patent barriers and facilitate early access.

The report concludes that inclusion of immune checkpoint inhibitors on the WHO EML can play an important role in catalysing global and national efforts to achieve equitable access by signalling the public health importance of immune checkpoint inhibitors and legitimizing and enabling policy and procurement strategies.

Price and cost–effectiveness data for the proposed immune checkpoint inhibitors were collected by the WHO Secretariat and included in the Evidence to Decision framework documents prepared by the Secretariat. Overall, the wholesale and retail prices for the proposed immune checkpoint inhibitors are still high across different World Bank income settings. Resource requirements to implement immune checkpoint inhibitor treatment were judged to be large for all medicine–indication pairings.

Cost–effectiveness studies were identified for each medicine–indication pairing but were limited to high-income and upper-middle-income settings. The reported incremental cost–effectiveness ratios were usually higher than corresponding willingness-to-pay thresholds, with few exceptions (e.g. pembrolizumab for dMMR/MSI-H colorectal cancer (*110*–*113*)).

Availability

No information was presented in the application on the availability of the proposed medicines.

The Evidence to Decision tables prepared by the Secretariat provided information about the availability of the proposed immune checkpoint inhibitors. Across the board, it was determined that they were probably not available in most settings. In each case, the medicines were approved for use in many countries, however access outside of high-income countries was deemed limited.

Data on the availability, out-of-pocket costs, and accessibility of pembrolizumab for melanoma, non-small cell lung cancer, colorectal cancer and renal cell carcinoma were available from the 2023 update to the ESMO Global Consortium Study (*114*). These data provide indirect evidence regarding the extent of immune checkpoint inhibitor availability across World Bank income settings. The study found that nivolumab and pembrolizumab for melanoma were almost always available to patients in high- and most upper-middle-income countries at no cost or on a subsidized basis. However, in low- and lower-middle-income countries, if available, these medicines were generally only available with full out-of-pocket costs paid by patients. Substantial discrepancies in accessibility of nivolumab and pembrolizumab were fund between higher and lower income countries.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee, as summarized below.

Biliary tract carcinoma irrespective of PD-L1 expression

The group did not support the inclusion of durvalumab plus chemotherapy for treatment of biliary tract cancer because of a small median overall survival gain (3.6 months, 95% CI 1.1 to 6.4 months) which was below the accepted EML threshold.

Cervical cancer with PD-L1 expression ≥ 1%

The group supported the inclusion of pembrolizumab plus chemotherapy (without bevacizumab) for the treatment of cervical cancer with PD-L1 expression ≥ 1% based on a median overall survival gain of 11 months (95% CI 5.8 to 17.2 months) based on long-term follow-up (median 39.1 months). The group considered that the subgroup analysis comparing overall survival in patients with or without concomitant bevacizumab found no meaningful difference between treatment groups (HR 0.63, 95% CI 0.47 to 0.87 and HR 0.74, 95% CI 0.53 to 1.04, respectively).

dMMR/MSI-H colorectal cancer

The group supported the inclusion of pembrolizumab as monotherapy for dMMR/MSI-H colorectal cancer based on a median overall survival gain of 12.9 months (95% CI –1.07 to 32.3 months) based on long-term follow-up (median 44.5 months). Additional benefits identified include a small increase in health-related quality of life and a moderate decrease in adverse events compared with chemotherapy.

The group did not support the inclusion of nivolumab plus ipilimumab for this indication because the added value of ipilimumab and nivolumab together was judged to be limited. Furthermore, the group had concerns about the price of two versus one immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines.

dMMR/MSI-H endometrial cancer

The group did not support the inclusion of dostarlimab plus chemotherapy for treatment of dMMR/MSI-H endometrial cancer. It noted that the calculated increase in median overall survival was extremely large (66.7 months, 95% CI 18.4 to 153.3 months), and that dostarlimab may be associated with a small improvement in health-related quality of life. However, the group had concerns over the price and duration of treatment, which would be prohibitively high in most

settings. The group also noted that data for pembrolizumab plus chemotherapy were promising but immature at this time. It also raised concerns over lack of access to backbone chemotherapy (carboplatin and paclitaxel) in some settings.

HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 5

The group did not support the inclusion of pembrolizumab plus chemotherapy or nivolumab plus chemotherapy for treatment of HER2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 expression CPS ≥ 1 (pembrolizumab) or CPS ≥ 5 (nivolumab) because of affordability concerns, limited median overall survival gains, little to no difference in health-related quality of life and possible increases in adverse events.

Head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1

The group did not support the inclusion of pembrolizumab chemotherapy for treatment of head and neck squamous cell carcinoma with PD-L1 expression CPS ≥ 1. The group noted that the medicines offer a moderate overall survival gain of 6 months. However, it considered that patients often have worse performance status (e.g. ECOG 2/3) outside of clinical trials and, in such patients, pembrolizumab has been associated with less pronounced improvements in overall survival (*115*).

Hepatocellular carcinoma irrespective of PD-L1 expression

The group did not support the inclusion of atezolizumab plus bevacizumab, durvalumab monotherapy, or durvalumab plus tremelimumab for treatment of hepatocellular carcinoma. All trials compared immune checkpoint inhibitors with sorafenib, a tyrosine kinase inhibitor that is not currently listed as an essential medicine and may be the best treatment option and thus may not be an appropriate comparator. Only atezolizumab plus bevacizumab met the EML threshold for overall survival gain. The duration of follow-up and median overall survival gains varied across the trials. The group interpreted this heterogeneity as a factor that limited the generalizability of benefit across the medicines.

Malignant melanoma

The cancer experts did not support the inclusion of nivolumab plus ipilimumab for treatment of malignant melanoma irrespective of PD-L1 expression or *BRAF* V600-mutation status. The group judged that combination therapy, when compared with monotherapy, had long-lasting and large benefits in overall survival (median overall survival 12.8 months after median follow-up of 34.6 months). However, this benefit was offset by concerns regarding the increased

price and adverse events with combination therapy compared with nivolumab or pembrolizumab monotherapy (already included on the EML). Despite being beneficial, the group considered that the addition of ipilimumab to nivolumab would present a further challenge in a number of settings (cost of two versus one immune checkpoint inhibitors and the additional burden of procuring and administering multiple medicines) and interfere with the priority of the large-scale adoption of nivolumab or pembrolizumab.

Given the dominant role of pembrolizumab in the treatment of malignant melanoma and other cancers, the group proposed reversing the current listing of nivolumab as the class representative and pembrolizumab as the therapeutic alternative on the EML. The group also suggested that an application for pembrolizumab and nivolumab to be included on the EMLc for the treatment of malignant melanoma in children be sought in the future.

Oncogenic driver wild-type non-small cell lung cancer

The group supported the inclusion of pembrolizumab, atezolizumab and cemiplimab as monotherapy for oncogenic-driver wild-type non-small cell lung cancer with PD-L1 expression ≥ 50% but were unable to reach consensus on whether or not to support the inclusion of tislelizumab plus chemotherapy for this indication.

Median overall survival benefits for pembrolizumab, atezolizumab, cemiplimab, and tislelizumab plus chemotherapy were 6.3 months, 3.7 months, 8.0 months and 4.5 months, respectively. The group noted that the survival gain with atezolizumab might have been underestimated, given that a proportion of trial participants received immune checkpoint inhibitors in the subsequent line of treatment. The group noted that evidence on and regulatory approval for tislelizumab monotherapy for non-small cell lung cancer is lacking.

The group did not support the inclusion of cemiplimab plus chemotherapy, durvalumab plus tremelimumab plus chemotherapy, nivolumab plus ipilimumab plus chemotherapy or pembrolizumab plus chemotherapy for treatment of oncogenic-driver wild-type non-small cell lung cancer irrespective of PD-L1 expression.

The decision to support the inclusion of monotherapy over combination therapy was based on the strong biological rationale that patients with increased PD-L1 expression are likely to benefit more and the potential to avoid cytotoxic effects from chemotherapy.

The group raised concerns over the feasibility of using immune checkpoint inhibitors in low-income settings because of the need for companion diagnostic tests to identify patients eligible for treatment (i.e. with PD-L1 expression ≥ 50% and without targetable oncogenes). However, feasibility is more variable in middle-income settings where diagnostic testing is more readily available and the price of testing is a small fraction of the overall treatment cost.

Some members of the group emphasized that immune checkpoint inhibitors for non-small cell lung cancer are likely not cost-effective in most settings, and their use risks diverting resources at the expense of other essential medicines. However, by supporting the inclusion only of monotherapy in patients with high PD-L1 expression, countries can be guided in prioritizing these medicines for the indications and in the populations for whom the benefits would be the largest.

Oesophageal squamous cell carcinoma with PD-L1 expression CPS ≥ 1/CPS ≥ 10

The group did not support the inclusion of pembrolizumab plus chemotherapy for treatment of oesophageal squamous cell carcinoma with PD-L1 expression ≥ 10%. It also did not support the inclusion of nivolumab plus chemotherapy or nivolumab plus ipilimumab plus chemotherapy for treatment of oesophageal squamous cell carcinoma with PD-L1 expression ≥ 1%. The group judged that the gains in overall survival with these combinations were moderate in size, but that the benefits were offset by the price, uncertainty in response durability, the unclear role of PD-L1 expression as a predictive biomarker and the potential for increased harms associated with poorer prognosis at baseline. The group considered that pembrolizumab, nivolumab and nivolumab plus ipilimumab are likely the least cost-effective options for this indication when compared with tislelizumab and toripalimab, for which separate applications were evaluated.

Renal cell carcinoma irrespective of PD-L1 expression

The group did not support the inclusion of nivolumab plus ipilimumab, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib for treatment of renal cell carcinoma versus sunitinib because of heterogeneity in the trial results and concerns over cost–effectiveness outside of high-income countries. There was also uncertainty about the optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (e.g. in sequence or in combination). The group noted that the addition of a tyrosine kinase inhibitor to pembrolizumab monotherapy probably increased adverse events.

Triple-negative breast cancer with PD-L1 expression ≥ 10%

The group did not support the inclusion of pembrolizumab plus chemotherapy for treatment of triple-negative breast cancer because of heterogeneity in trial results, concerns over cost–effectiveness outside of high-income countries and feasibility due to diagnostic requirements. The group judged that the overall survival gain were moderate (6.0 months), but also noted evidence from a phase III trial of chemotherapy with or without atezolizumab for early relapsing unresectable locally advanced or metastatic triple-negative breast cancer, which found no overall survival benefit with atezolizumab-based treatment (*116*).

Strategies to improve access to immune checkpoint inhibitors

The group emphasized the importance of strategies to improve access to cancer medicines and discussed a number of strategies including: the potential for a pharmacological class effect and interchangeability of immune checkpoint inhibitors; reduced intensity of dosing and overall treatment duration; vial sharing; biosimilars; pooled procurement; and licensing strategies to improve access and reduce global inequities.

Interchangeability of immune checkpoint inhibitors

In the absence of head-to-head randomized trials, the group considered strong biological rationale and indirect evidence supporting the potential for recommending different immune checkpoint inhibitors as therapeutic alternatives and therapeutically equivalent, to set up tendering mechanisms for procurement agencies and hospitals (*117*, *118*). PD-1 and PD-L1 inhibitors act to prevent the same immunological interaction that occurs between the PD-1 receptor on T-cells and the PD-L1 protein on tumour cells, which otherwise suppresses the immune system's ability to attack tumour cells (*119*).

In consideration of metastatic non-small cell lung cancer, the group highlighted the effects of pembrolizumab, atezolizumab and cemiplimab on overall survival, and considered that any differences in trial results may be attributed to differences in the study design and population, and not to inherent differences between the medicines (*51*, *56*, *58*, *61*). Therefore, the cancer experts supported the inclusion, suggesting pembrolizumab be listed as the class representative, with atezolizumab and cemiplimab as therapeutic alternatives. The group proposed that in cases where pembrolizumab, atezolizumab or cemiplimab are not available or affordable, other immune checkpoint inhibitors could also be considered as therapeutic alternatives at the country level since they act on the same immunological pathway. However, the magnitude of clinical benefit should also be taken into consideration and therapeutic equivalence may therefore be limited to cancer medicines and indications in which the magnitude of benefit is large and the evidence is mature. These medicines should be prioritized for procurement.

The group highlighted the need to improve current standards for regulatory approval and suggested comparative adaptive trials as the new standard to prove equivalence and interchangeability among the various immune checkpoint inhibitors. This research should include head-to-head randomized trials – as recently suggested by the United States Food and Drug Administration – to reduce heterogeneity in study designs and enable comparisons (*120*). The PERLA trial is one example of a head-to-head randomized trial that provided evidence for similar efficacy of dostarlimab combined with chemotherapy and pembrolizumab combined with chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer (*121*). With indirect evidence, heterogeneity in

techniques and tests measuring levels of predictive biomarkers limits confidence in indirect comparisons of immune checkpoint inhibitors. Finally, post-approval studies can provide important information on optimal treatment doses, schedules, duration and positions (e.g. first- versus second-line) (*119*).

Reduced intensity treatment

The group acknowledged growing evidence supporting the use of reduced-intensity treatment with many molecules used to treat several types of cancer (*122*). Among immune checkpoint inhibitors, evidence indicates that much lower doses of both nivolumab and pembrolizumab provide maximal binding to their receptors, and that such binding is maintained for considerably longer than the registered dosing intervals of 2 or 4 weeks for nivolumab and 3 or 6 weeks for pembrolizumab.

A 2012 study investigated the binding of nivolumab to receptors on circulating T-cells at 8 weeks after a range of doses (0.1–10 mg/kg given every 2 weeks) and found no significant difference in receptor occupancy (*123*). The doses evaluated in cohorts of 10–20 patients were 3.3%, 10.0%, 33.3%, 100.0% and 333.3% of the clinically approved dose used in clinical trials evaluating the medicine. Only one outlier was found in 11 patients which had reduced binding at the very lowest dose of 0.1 mg/kg.

A 2024 study collected 122 serial peripheral blood mononuclear cell samples at multiple time points from 19 patients receiving nivolumab at different doses and at varying frequencies (every 4 to 12 weeks) (*124*). Receptor occupancy on CD4+ and CD8+ T-cells was measured at 4, 8 and 12 weeks after doses of 40 mg, 240 mg and 480 mg. No consistent differences were found in receptor binding either as a function of dose or time. Serum nivolumab concentration was measured as a function of time after these doses; although serum concentrations were higher with higher doses, the median serum concentration of low-dose (40 mg) nivolumab remained higher than the minimal effective concentration of 1.5 microgram/mL for 3 months.

In a phase II study, 168 patients with advanced renal cell cancer were randomized to receive nivolumab doses of 0.3 mg/kg, 2 mg/kg and 10 mg/kg every 3 weeks (*125*). No significant difference was seen in response rate, progression-free survival or overall survival between treatment groups, yet the dose taken forward for phase III trials was 3 mg/kg every 2 weeks.

A 2023 randomized phase III superiority study compared low-dose nivolumab (20 mg flat dose once every 3 weeks) combined with chemotherapy with chemotherapy alone in 151 patients with advanced head and neck squamous cell carcinoma (*126*). The approved dose of nivolumab for this indication is 240 mg every 2 weeks. Thus, every 6 weeks there was an intensity reduction between the on-label and low-dose of about 94% (40 mg versus 720 mg). The median overall survival at 1-year was 10.1 months and 6.7 months in the nivolumab and chemotherapy arms, respectively.

The consistent results of the target binding, pharmacokinetic and clinical studies provide substantial evidence in support of an alternative dosing strategy for nivolumab. This is especially important in settings where full-dose treatment is not attainable (e.g. due to out-of-pocket costs).

The approved doses of pembrolizumab are 2 mg/kg or a flat dose of 200 mg every 3 weeks, or double those doses given every 6 weeks. In a phase I study, an ex-vivo IL-2 PD-1 receptor modulation assay was used to study pembrolizumab receptor engagement after doses of 1 mg/kg, 3 mg/kg or 10 mg/kg every 2 weeks (*127*). PD-1 target engagement remained high during multiple courses of therapy and independent of dose. Intrapatient escalating doses of 0.005–10 mg/kg were given to patients and, with a terminal half-life of 2–3 weeks, measurements of serum concentration suggest that receptor inhibition would be maintained for at least 2 months after doses as low as 0.3 mg/kg.

The NVALT-30 trial evaluated low-dose pembrolizumab (300 mg every 6 weeks or 100 mg every 3 weeks, with or without chemotherapy) and standard dose pembrolizumab (400 mg every 6 weeks or 150–200 mg every 3 weeks) for treatment of stage IV non-small cell lung cancer (*128*). A pre-planned interim analysis found a non-significant difference in 1-year overall survival between dosing arms which met the predetermined criterion for continuing the trial.

Weight-based instead of fixed doses were shown to maintain treatment effectiveness while reducing treatment costs for non-small cell lung cancer in retrospective cohort studies and this dosing has been implemented in several countries (*129*–*131*).

Reduced-intensity treatment strategies include dose reduction, rounding and banding, longer intervals between administrations, and shorter duration of treatment. Multiple trials are investigating early cessation of treatment, extended dosing intervals and lower doses as reduced-intensity treatment strategies for immune checkpoint inhibitors (*132*, *133*). The cancer experts' group considered that promising data were available for nivolumab and pembrolizumab based on dose-finding phase I and II studies (*125*–*127*, *134*, *135*), and pharmacokinetic and pharmacodynamic studies (*123*, *124*, *133*, *136*–*140*). However, limited data were available that demonstrated similarity with registered doses based on long-term overall survival from comparative randomized trials, as well as for other immune checkpoint inhibitors. The group considered that reduced-intensity treatment has the potential to significantly reduce the cost of immune checkpoint inhibitor treatment, without substantial reduction in efficacy. The group recommended that emerging evidence from ongoing and future dose-optimization trials should be closely monitored.

Vial size and sharing

Immune checkpoint inhibitors are typically provided in single-use vials with fixed concentrations and unused portions often go to waste if the entire vial is not

needed for an individual patient's dose. Vial sharing is a practical approach to cut costs and improve access. Vial sharing allows for precise doses to be administered without wastage, particularly in weight-based regimens (*141*). Some regions have strict rules about the sharing of single-use vials due to contamination risks. However, controlled hospital settings with proper aseptic techniques can mitigate these concerns. Such a strategy may also require coordination in scheduling and pharmacy preparation to ensure vials are used efficiently with multiple patients within the drug stability timeframes.

Biosimilars, pooled procurement and licensing strategies

The group agreed with and endorsed the findings of the report describing an analysis of financial implications of pembrolizumab and nivolumab and the potential impact of their inclusion on the EML (*108*), elaborated in Costs/cost-effectiveness subsection above.

Alternative models for stimulating medicine innovation

The group highlighted that the high prices of new cancer medicines are not justified by production costs, disease rarity or magnitude of benefit. Efforts to use collective purchasing power through negotiations with procurement or reimbursement authorities, or through price controls, have had limited success in moderating excessive prices and disparities in access. The group noted various innovative models for medicines development. These included proposals aimed at: facilitating rapid entry of generics in developing countries by offering a system of rewards for originator companies (*142*); and investigating alternative models for funding and investment that delink the costs of research development and the price of health products (*143*, *144*).

Committee recommendations

The Expert Committee recognized that cancer is a growing societal, public health and economic problem globally, and it is responsible for nearly one in three premature deaths from noncommunicable disease. The proportion of patients with advanced stage at first presentation is still substantial. Solid tumours that are amenable to effective therapy using PD-1/PD-L1 immune checkpoint inhibitors are a major cause of the rising burdens with respect to lives lost. The Committee recalled previous applications for immune checkpoint inhibitors. In 2019 nivolumab and pembrolizumab were recommended for listing for treatment of metastatic melanoma, a relatively rare cancer for which these medicines are extremely effective. In 2021 and 2023, applications for immune checkpoint inhibitors for treatment of metastatic NSCLC were not recommended, despite recognition of their relevant efficacy in prolonging life, due to their high costs. The Committee noted the rapid pace of innovation in immuno-oncology and

emphasized the importance of reducing inequities in cancer care by increasing access to immune checkpoint inhibitors, adopting multiple strategies.

In consideration of the application, the Expert Committee:

- appreciated the approach taken by the WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies at the University of Cologne, Germany to identify the PD-1/PD-L1 immune checkpoint inhibitor–indication pairings proposed for EML listing from among the many such medicines that are approved and available, and considered that the approach taken was up-to-date, comprehensive, systematic, transparent and evidence based and provided a solid basis for its decision-making;
- noted that all proposed pairings were approved by the European Medicines Agency for first-line treatment of adults for the therapeutic indications for which they are proposed, had evidence from randomized trials and received a score of four or higher on the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale in the non-curative setting;
- applied the EML principle for cancer medicines to demonstrate at least 4–6 months overall survival gain in randomized controlled trials; and
- appreciated and took into consideration the review of the application undertaken by the EML Cancer Experts group and the Evidence to Decision frameworks that followed the GRADE approach prepared by the Secretariat.

The Committee favoured pairings where the evidence strongly supported a large benefit-to-risk ratio. The Committee considered monotherapy more positively than combination therapy for indications where both are approved and a trade-off between additional efficacy, toxicity and cost would typically occur.

The Expert Committee recommended the inclusion of:

- pembrolizumab, atezolizumab and cemiplimab as first-line monotherapy of metastatic non-small cell lung cancer with high PD-L1 expression (≥ 50%). Listing is recommended for pembrolizumab with a square box as the class representative, and atezolizumab and cemiplimab as specified therapeutic alternatives;
- pembrolizumab as first-line monotherapy for deficient mismatch repair/microsatellite instability-high metastatic colorectal cancer;
- pembrolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic cervical cancer with PD-L1 expression ≥ 1%.

The Committee considered that these recommendations for inclusion provide the best chance of minimizing financial harm and concentrating expenditure into the areas with the most favourable incremental gain in benefit-to-risk ratio. The Committee noted that the use of immune checkpoint inhibitors in adults with solid tumours that have predictive biomarkers (e.g. high PD-L1 expression for non-small cell lung cancer) rather than all patients is the highest priority, to enable greater access in settings where budgetary constraints may require prioritization of scenarios that offer the greatest clinical value.

With the recommendation to list pembrolizumab for the above-mentioned indications, the Committee recommended changing the current square box listing of nivolumab as the class representative and pembrolizumab as the specified therapeutic alternative for metastatic melanoma, to make pembrolizumab the class representative with nivolumab as the specified therapeutic alternative. This is intended to signal to countries the possibility of aggregating procurement of a single molecule, pembrolizumab, for multiple cancer indications, which can influence price negotiations with manufacturers. Limiting procurement fragmentation by focusing on a select few immune checkpoint inhibitors is likely to facilitate central purchasing through competitive tendering and better competition from pembrolizumab biosimilars, thereby increasing access.

In addition to its recommendations on which immune checkpoint inhibitors to prioritize for inclusion on the EML, the Committee also recognized the value of strategies to improve access, particularly in resource-constrained settings, as presented in the report from the EML cancer experts consultation meeting, and recommended their use. The Committee noted that these strategies were based on evaluation of available evidence and pragmatic considerations. The Committee considered the strategies to improve access to care in two components: clinical strategies and health-system strategies. The Committee acknowledged that, while clinical strategies (over which doctors and patients have greater control) and health-system strategies (requiring government-led policy legislations and reforms) should complement each other, clinical strategies can be implemented immediately and can rapidly benefit access.

Clinical strategies – doctors and patients

The Committee acknowledged the importance of patients being empowered to make an informed and consensual decision about their treatment, including through information on benefits, harms, accessibility and feasibility of care. This might require comparing alternatives that may differ from each other in one or more of the aforementioned factors. Strategies that can be considered to improve access include: dose optimization according to patient weight (weight-based dosing); rounding down doses to the closest vial size and strength (dose banding); or hybrid dosing regimens that combine the two; and if relevant, vial sharing.

Additionally, longer intervals between treatment administration or shorter durations of treatment can also be considered. The Committee also noted that ongoing studies are investigating outcomes with ultra-low-dose immunotherapy. If the results are favourable, ultra-low-dose immunotherapy could be a viable strategy to further improve access.

Health-system strategies – policy-makers

To enable better value procurement through tendering and competition leading to increased access for individuals and health systems, the Committee recommended that national policies take advantage of similar clinical performance in different immune checkpoint inhibitors, regardless of their biological target (i.e. PD-1 or PD-L1). The Committee opted to recommend four immune checkpoint inhibitors for non-small cell lung cancer using the square box listing, indicating interchangeability at the health-system level for this indication. The recommended medicines have different pharmacological properties but are considered therapeutic alternatives. Where no relevant difference exists in efficacy and safety data, the preferred medicine at the country level should be the one that is generally available at the lowest price. At the country level, the interpretation of the square box should be extensive (i.e. a class effect), potentially covering other equally effective and safe immune checkpoint inhibitors of assured quality where these are offered at an advantageous price.

The Committee stressed the importance of effective strategies to encourage rapid entry of biosimilars of immune checkpoint inhibitors into markets. With pembrolizumab listed on the EML for multiple cancers, efforts should be prioritized on accelerating approval and procurement of pembrolizumab biosimilars over those of the other listed medicines. Ensuring a competitive market, with ideally more than four or five alternative suppliers, would foster market maturity, reduce prices, and strengthen the sustainability of access. This strategy is fully aligned with WHO's broader goal of encouraging generic and biosimilar competition as a central pathway to achieving equitable access to high-value cancer treatments.

The Committee recognized the need for companion in-vitro diagnostic tests to identify patients eligible for treatment with the recommended immune checkpoint inhibitors. It noted that access to diagnostic capacity is limited in less-resourced settings and may be a barrier to appropriate and optimal use of these medicines. However, the Committee highlighted that this scenario was more variable in middle-income countries, where testing for molecular alterations is more readily available and the price associated with tests is a small fraction of the price associated with treatment. The Committee recognized that the requirement for companion diagnostics adds additional cost but offers a pathway to limit inappropriate use of immune checkpoint inhibitors (i.e. outside of recommended indications) and serves to prevent the waste of resources with non-essential or lower-value use.

The Committee considered that countries could apply their own affordability criteria in determining which (if any) of the recommended immune checkpoint inhibitors could be reasonably incorporated into national EMLs and reimbursement schemes. In addition, the Committee considered that countries could apply their own feasibility criteria in assessing health-system readiness for implementing immune checkpoint inhibitors, in terms of diagnostic infrastructure, health-care worker training in immuno-oncology, resources for the management of immune-mediated side-effects and monitoring capabilities, to ensure their safe and effective use. The Committee recognized that the implementation of recommendations concerning immune checkpoint inhibitors will progress at different speeds, largely reflecting the capacity of individual healthcare systems. In low-income countries, limited resources, infrastructure challenges, and demographic factors such as a predominantly young population may significantly delay the adoption of these medicines. By contrast, upper- and lower-middle-income countries are expected to introduce them more rapidly.

The Expert Committee did not recommend listing for the following immune checkpoint inhibitors for treatment of the specified conditions:

- cemiplimab, durvalumab plus tremelimumab, nivolumab plus ipilimumab, or pembrolizumab – each in combination with chemotherapy – for the treatment of oncogenic-driver wild-type metastatic non-small cell lung cancer regardless of PD-L1 expression;
- tislelizumab in combination with chemotherapy for oncogenic-driver wild-type metastatic non-small cell lung cancer with ≥ 50% PD-L1 expression;
- nivolumab plus ipilimumab for the treatment of dMMR/MSI-H phenotype metastatic colorectal cancer or metastatic melanoma;
- dostarlimab in combination with chemotherapy for dMMR/MSI-H phenotype metastatic endometrial cancer;
- pembrolizumab or nivolumab, in combination with chemotherapy, for first-line treatment of metastatic ERBB2-negative gastric or gastro-oesophageal junction adenocarcinoma with ≥ 1% or ≥ 5% PD-L1 expression, respectively;
- durvalumab in combination with chemotherapy for first-line treatment of biliary tract cancer regardless of PD-L1 expression;
- durvalumab monotherapy, durvalumab plus tremelimumab, or atezolizumab plus bevacizumab for first-line treatment for metastatic hepatocellular carcinoma regardless of PD-L1 expression;
- pembrolizumab in combination with chemotherapy for first-line treatment of metastatic head and neck squamous cell carcinoma;

- pembrolizumab, nivolumab, or nivolumab plus ipilimumab, each in combination with chemotherapy, for first-line treatment of metastatic oesophageal squamous cell cancer;
- nivolumab plus ipilimumab, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib for the first-line treatment of metastatic renal cell carcinoma regardless of PD-L1 expression;
- pembrolizumab in combination with chemotherapy for first-line treatment of triple-negative breast cancer with PD-L1 expression CPS ≥ 10.

The reasons for not recommending inclusion of these pairings included prioritization of monotherapy over combination therapy, magnitude of overall survival gains of fewer than 4–6 months, limited or absence of mature overall survival data, unfavourable benefit-to-risk profiles, uncertainty about optimal immune checkpoint inhibitor and tyrosine kinase inhibitor positioning (i.e. in sequence or in combination) and uncertainty about optimal use across different patient cohorts which may vary with the immunogenicity of tumour types.

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Tislelizumab – addition – EML

Tislelizumab **ATC code: L01FF09**

Proposal

Addition of tislelizumab to the complementary list of the EML for treatment of unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults as first-line therapy in combination with chemotherapy, and as second-line monotherapy.

Applicant

BeiGene Ltd, Cambridge, MA, United States of America

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments the application. The team did not support the inclusion of tislelizumab on the EML for oesophageal squamous cell carcinoma because of inconclusive and potentially limited clinical efficacy.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Concentrate solution for infusion: 100 mg/10 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Tislelizumab has not previously been considered for inclusion on the Model List for the treatment of oesophageal squamous cell carcinoma.

An application for the addition of toripalimab to the EML for treatment of oesophageal squamous cell carcinoma was considered by the Expert Committee in 2023. The Committee acknowledged that the addition of toripalimab to

chemotherapy might be associated with relevant improvements in survival compared with chemotherapy alone, however, the evidence was immature with short follow-up. Although the Committee acknowledged the promising role of chemoimmunotherapy in the treatment of this cancer, listing was not recommended. The Committee recommended that the evidence for these treatments continue to be monitored for potential future EML consideration (*1*).

There are currently no medicines included on the Model List for the treatment of oesophageal squamous cell carcinoma.

Public health relevance

According to Globocan, in 2022 there were 511 054 incident oesophageal cancer cases and 445 391 deaths worldwide (*2*). Oesophageal cancer can be categorized into two main histological subtypes with different etiologies: adenocarcinoma and squamous cell carcinoma. Globally, squamous cell carcinoma was the most common subtype in both male and female patients, contributing to 85% of all oesophageal cancer cases (*3*). Oesophageal cancer shows substantial geographical variance, with Asia accounting for around 75% of the global incidence, mortality and 5-year prevalence (*2*).

According to the Global Burden of Disease study, in 2021, oesophageal cancer was responsible for almost 540 000 deaths globally, and almost 13 million disability-adjusted life years (*4*).

Summary of evidence: benefits

The application identified nine published systematic literature reviews including tislelizumab for treatment of unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma. In all these reviews, the only randomized controlled trials that included a tislelizumab treatment arm were the pivotal trials conducted by the applicant: RATIONALE-306 in first-line treatment (*5*) and RATIONALE-302 in second-line treatment (*6*).

First-line treatment

A 2024 systematic review and network meta-analysis of seven randomized controlled trials (4688 participants) evaluated the efficacy and safety of first-line immunotherapy for advanced oesophageal squamous cell carcinoma (*7*). Pooled analysis showed that immunotherapy agents were associated with significantly prolonged overall survival compared with chemotherapy alone, irrespective of programmed death-ligand 1 (PD-L1) expression (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.62 to 0.74), including tislelizumab (HR 0.68, 95% CI 0.56 to 0.82) which ranked third in prolonging overall survival after toripalimab and sintilimab. Similarly, all immunotherapy agents evaluated were associated with significantly prolonged progression-free survival, irrespective of

PD-L1 expression (HR 0.62, 95% CI 0.57 to 0.67), including tislelizumab (HR 0.62, 95% CI 0.52 to 0.74), which ranked fourth after camrelizumab, sintilimab and toripalimab. No significant differences were seen between tislelizumab and pembrolizumab, nivolumab, nivolumab plus ipilimumab or toripalimab for overall survival or progression-free survival.

A second systematic review and network meta-analysis in 2024 of nine randomized controlled trials (4499 participants) also evaluated the efficacy and safety of first-line immunotherapy for advanced oesophageal squamous cell carcinoma (*8*). This review included the same randomized controlled trials involving immunotherapies as the above-mentioned review, plus one randomized controlled trial comparing capecitabine plus paclitaxel versus capecitabine plus cisplatin, and one randomized controlled trial comparing cetuximab plus chemotherapy with cisplatin plus 5-fluoropurimidine. In this review, tislelizumab ranked fourth for overall survival and progression-free survival.

Another 2024 systematic review performed a survival analysis of immunotherapy-based therapies in first-line treatment of oesophageal squamous cell carcinoma using reconstructed patient-level data (*9*). The same seven randomized controlled trials involving immunotherapies as the previous reviews were included. The study reported that tislelizumab, toripalimab and sintilimab had the best overall survival performance of the seven immunotherapies evaluated, with median overall survival of 17.2 months, 17.0 months and 16.7 months, respectively. Median overall survival for nivolumab and pembrolizumab was 13.2 months and 12.6 months , respectively. For progression-free survival, sintilimab (median progression-free survival 7.2 months) and tislelizumab (median progression-free survival 7.3 months) were superior to other regimens.

A 2023 systematic review and network meta-analysis of 17 randomized controlled trials (9128 participants) evaluated the efficacy and safety of 19 treatment regimens involving immunochemotherapy, immunotherapy, chemotherapy and targeted therapy as first-line treatment for advanced and metastatic oesophageal cancer (*10*). Consistent with previous reviews, chemoimmunotherapy was associated with improvements in overall survival and progression-free survival compared with chemotherapy alone. For overall survival, toripalimab, sintilimab and tislelizumab ranked first, second and third, respectively.

Another 2023 systematic review and network meta-analysis of six randomized controlled trials (3611 participants) also evaluated the efficacy and safety of first-line chemoimmunotherapy for advanced oesophageal squamous cell carcinoma (*11*). This review did not include the ASTRUM-007 trial of serplulimab included in the previous reviews. Findings were generally consistent with the findings of the previous reviews.

RATIONALE-306 is a phase III randomized, double-blind, placebo-controlled, multicentre study comparing the safety and efficacy of tislelizumab

plus chemotherapy versus chemotherapy alone (5, 12). Participants were randomized 1:1 to receive tislelizumab plus chemotherapy ($n = 326$) or placebo plus chemotherapy ($n = 323$). A total of 146 participants in the tislelizumab plus chemotherapy arm and 144 participants in the placebo plus chemotherapy arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with fluoropyrimidine (5-fluorouracil/capecitabine). The remaining participants received platinum (cisplatin/oxaliplatin) with paclitaxel. At the interim analysis from the 28 February 2022 cut-off, tislelizumab plus chemotherapy was associated with significantly superior overall survival compared with chemotherapy alone (median overall survival 17.2 months versus 10.6 months; HR 0.66, 95% CI 0.54 to 0.80) (5). At an extended 3-year follow-up from the 24 November 2023 data cut-off, median overall survival was 22.1 months versus 14.1 months; HR 0.70, 95% CI 0.59 to 0.83) (12). Overall survival benefits were observed in all prespecified subgroups (choice of chemotherapy, baseline PD-L1 expression, geographic region, performance status, age, sex and smoking status).

Second-line treatment

The application identified four systematic reviews and network meta-analyses that assessed immunotherapies versus chemotherapy as second-line treatment of advanced oesophageal squamous cell carcinoma (13–16). Details of the reviews and their findings were not presented in the application. The application stated that consensus existed across all the reviews identified that there were statistically significant and clinically meaningful improvements in overall survival with tislelizumab monotherapy compared with chemotherapy. In addition, the application stated that where tislelizumab was compared with other PD-1 inhibitors in the second-line setting, it showed comparable progression-free survival and was "particularly efficacious".

RATIONALE-302 is a phase III randomized, open label study of tislelizumab monotherapy versus chemotherapy as second-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (6). Participants were randomized 1:1 to receive tislelizumab ($n = 256$) or chemotherapy (paclitaxel, docetaxel or irinotecan) ($n = 256$). At the 1 December 2020 data cut-off, tislelizumab was associated with significantly superior overall survival compared with chemotherapy (median overall survival 8.3 months versus 6.3 months; stratified HR 0.70, 95% CI 0.57 to 0.85). Median progression-free survival as assessed by the study investigator was 1.6 months and 2.1 months in the tislelizumab and chemotherapy arms, respectively (stratified HR 0.83, 95% CI 0.67 to 1.01). Overall survival benefits were observed across all predefined subgroups (choice of chemotherapy, baseline PD-L1 expression, geographic region, performance status, age, sex and smoking status).

Summary of evidence: harms

Pooled analysis in the first 2024 systematic review and network meta-analysis previously described showed that the use of immunotherapy with chemotherapy was associated with a greater incidence of grade 3 or higher adverse events compared with chemotherapy alone (risk ratio (RR) 1.04, 95% CI 1.00 to 1.09). Individually, only camrelizumab and nivolumab plus ipilimumab were associated with a reduced risk of grade 3 or higher adverse events. Tislelizumab ranked fifth for this outcome (RR 1.10, 95% CI 0.80 to 1.52). Commonly reported treatment-related adverse events included anaemia, decreased white-cell count, nausea, vomiting, decreased neutrophil count, alopecia, asthenia, decreased appetite, decrease platelet count and diarrhoea. Frequently reported immune-mediated adverse events included rash, hypothyroidism, hyperthyroidism, immune-mediated lung disease, pruritus and pneumonitis (*7*). Where reported, the other systematic reviews presented consistent findings.

At the 3-year follow-up of RATIONALE-306, the incidence of any grade, and grade ≥ 3 treatment-related adverse events were comparable between treatment groups. Serious treatment-related adverse events and treatment-emergent adverse events leading to treatment discontinuation occurred more frequently in the tislelizumab arm. The most common treatment-related adverse events of grade ≥ 3 were decreased neutrophil count (30.9% versus 32.7%), anaemia (14.8% versus 12.8%) and decreased white blood cell count (10.8% versus 15.6%). Health-related quality of life was comparable between treatment groups (*12*).

In RATIONALE-302, treatment-related adverse events were reported in 73.3% and 93.8% of participants in the tislelizumab and chemotherapy arms, respectively. Grade ≥ 3 treatment-related adverse events were reported in 18.8% and 55.8% of participants in the tislelizumab and chemotherapy arms, respectively. The incidence of serious treatment-emergent adverse events was similar between treatment groups (41.2% versus 43.8%). Participants receiving tislelizumab showed more favourable quality of life outcomes compared with participants receiving chemotherapy (*6*).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of oesophageal squamous cell carcinoma are not currently available.

Costs/cost–effectiveness

The application identified nine cost–effectiveness analyses for tislelizumab in first- (*17*–*23*) and second-line (*13*, *24*) therapy of advanced or metastatic oesophageal squamous cell carcinoma. All included data from RATIONALE-306 or study populations consistent with RATIONALE-306, had a 10- or 12-year time horizon and were conducted from the Chinese health-system perspective.

Among the economic analyses for tislelizumab plus chemotherapy versus chemotherapy alone in the first-line setting, incremental cost–effectiveness ratios ranged from 18 846 United States dollars (US$) to US$ 34 699 per quality-adjusted life year (QALY) gained. One study considered multiple programmed cell death protein 1 (PD-1) inhibitors in first-line treatment (*23*). The resultant base-case incremental cost–effectiveness ratios per QALY gained were US$ 21 771 for sintilimab, US$ 22 694 for toripalimab, US$ 24 853 for camrelizumab, US$ 25 973 for tislelizumab, US$ 107 042 for serplulimab, US$ 183 825 for nivolumab and US$ 256 937 for pembrolizumab.

One study conducted an economic evaluation of tislelizumab versus chemotherapy as second-line therapy using data from RATIONALE-302 (*24*). The resultant incremental cost–effectiveness ratio was US$ 11 073 per QALY gained. Another study considered the cost–effectiveness of five PD-1 inhibitors versus chemotherapy in the second-line setting (*13*). The resultant base-case incremental cost–effectiveness ratios per QALY gained were US$ 4724 for sintilimab, US$ 8913 for tislelizumab, US$ 13 549 for camrelizumab, US$ 170 710 for nivolumab and US$ 269 654 for pembrolizumab. In sensitivity analyses, medicine prices had the greatest impact on the outcomes.

Availability

The application reported that tislelizumab has regulatory approval in China and Thailand for use in combination with chemotherapy as first-line treatment of patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma. Regulatory approval submissions in Australia, Europe, Indonesia, Japan, Republic of Korea, Singapore, Switzerland and United States were under review at the time of submission.

The application reported that tislelizumab has regulatory approval in Australia, Brazil, China, Europe, Hong Kong, Israel, Republic of Korea, Singapore, Switzerland, Thailand, United Kingdom of Great Britain and Northern Ireland and United States as monotherapy for second-line treatment of unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma. Regulatory approval submissions in India, Japan, Malaysia and New Zealand were under review at the time of submission.

Tislelizumab is currently under patent protection and no generic versions are available.

Other considerations

Tislelizumab was one of five immune checkpoint inhibitors evaluated for the treatment of oesophageal squamous cell carcinoma during the Expert Committee meeting. Other immune checkpoint inhibitors evaluated were ipilimumab plus nivolumab, nivolumab (plus chemotherapy) and pembrolizumab (plus chemotherapy) (application A.22), and toripalimab (plus chemotherapy) (application A.28).

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of tislelizumab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma. The group considered that the reported gains in overall survival were moderate in size and offset by the unclear role of PD-L1 expression as a predictive biomarker. Long-term data across the class of immune checkpoint inhibitors are lacking.

Committee recommendations

The Expert Committee recognized the significant public health burden of oesophageal squamous cell carcinoma, particularly in Asia where the disease is considered endemic and its incidence and prevalence and the mortality it causes are disproportionately high, accounting for about 75% of the global burden. The Committee noted the availability of tislelizumab in regions most affected by this disease.

The Committee considered evidence from tislelizumab clinical trials that showed an overall survival benefit of about 6 months for tislelizumab plus chemotherapy compared with chemotherapy alone in the first-line setting. In the later-line setting, tislelizumab monotherapy was associated with an overall survival benefit of only 2 months compared with chemotherapy, which is below the established 4–6 month threshold for the EML.

The Committee considered the comparative effectiveness of tislelizumab and other immune checkpoint inhibitors for oesophageal squamous cell carcinoma in the first-line setting and found that the magnitudes of effect on overall survival were relatively consistent at about 6 months overall survival gain compared with chemotherapy, which the Committee judged to be moderate. In each case, treatment was in combination with chemotherapy. The Committee considered that this finding suggested a class effect and there was potential for medicines within the class to be considered as therapeutic alternatives.

The Committee agreed with the EML cancer expert group that the role of PD-L1 expression as a predictive biomarker for benefit was unclear. The Committee also noted the lack of long-term survival data across the class of immune checkpoint inhibitors. As regards harms, the Committee noted the

potential for increased harm associated with a poorer prognosis at baseline and the concomitant use of chemotherapy.

The Committee noted that tislelizumab was likely to be a more cost-effective option compared with pembrolizumab, nivolumab and nivolumab plus ipilimumab, but not toripalimab. However, the Committee considered that the cost of treatment may still have a substantial budget impact, particularly in resource-constrained settings.

Based on these considerations, the Expert Committee did not recommend the inclusion of tislelizumab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma in the first- or later-line setting. In terms of the medicine class, the Committee considered that ongoing trials and determination of the role of PD-L1 expression as a predictive biomarker will be informative for future consideration of these medicines for this indication.

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Toripalimab – addition – EML

Toripalimab **ATC code: L01FF13**

Proposal

Addition of toripalimab to the complementary list of the EML for treatment of metastatic or recurrent, locally advanced nasopharyngeal carcinoma and metastatic or recurrent oesophageal squamous cell carcinoma in combination with chemotherapy.

Applicant

Shanghai Junshi Biosciences Co. Ltd, Shanghai, China

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team highlighted that overall survival data for toripalimab were still insufficiently mature and advised that further consideration could be made as additional studies are reported.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Concentrate solution for infusion: 240 mg/6 mL in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application for the addition of toripalimab to the EML for treatment of nasopharyngeal carcinoma and oesophageal squamous cell carcinoma was considered by the Expert Committee in 2023. The 2023 Committee's recommendations are presented below.

The 2023 Expert Committee acknowledged the global health burden of nasopharyngeal and oesophageal cancers and noted the endemic nature of nasopharyngeal cancer in low- and middle-income countries. The Committee agreed that better therapeutic options were needed for treatment of these cancers.

The Committee noted that the evidence presented in the application focused on patients with metastatic or recurrent, locally advanced disease and that the patients included in the trials were not selected based on the level of tumour expression of PD-L1, although this aspect was explored in post hoc analyses based on aggregated data from multiple randomized controlled trials on oesophageal cancer. The Committee considered that more evidence analysing the effect of treatment based on PD-L1 expression or other biomarkers would be informative to understand whether a particular subgroup of patients might benefit more from treatment.

The Committee considered that the benefits observed when toripalimab was added to chemotherapy in the first-line treatment for advanced nasopharyngeal cancer were modest, and that toripalimab was assigned a score of 3 on the European Society for Medical Oncology (ESMO) magnitude of clinical benefit scale, which is lower than the accepted threshold for EML consideration.

For advanced oesophageal squamous cell cancer, the Committee acknowledged that the addition of toripalimab to chemotherapy might be associated with relevant improvements in survival compared with chemotherapy alone, although the evidence is still immature, with short follow-up. A score on the ESMO magnitude of clinical benefit scale is not available for toripalimab for this indication.

The Committee acknowledged that the reported price of toripalimab was considerably lower than other immune checkpoint inhibitors However, the price estimates were only available from China, the only country where toripalimab is currently marketed.

The Expert Committee therefore did not recommend the inclusion of toripalimab on the complementary list of the EML for the treatment of nasopharyngeal and oesophageal squamous cell carcinomas. The Committee acknowledged the promising role of chemoimmunotherapy in the treatment of these cancers and recommended that the evidence for these treatments continue to be monitored for potential future EML consideration (*1*).

Public health relevance

Nasopharyngeal carcinoma

According to Globocan, in 2022 there were 120 434 incident cases and 73 482 deaths worldwide from nasopharyngeal carcinoma. The incidence, mortality and 5-year prevalence vary substantially by geographical region, with Asia accounting for almost 85% (*2*).

Oesophageal squamous cell carcinoma

According to Globocan, in 2022 there were 511 054 incident cases of oesophageal cancer and 445 391 deaths worldwide (*3*). Oesophageal cancer can be categorized into two main histological subtypes with different etiologies: adenocarcinoma and squamous cell carcinoma. Globally, squamous cell carcinoma is the most common subtype in both male and female patients, contributing to 85% of all oesophageal cancer cases (*4*). Oesophageal cancer shows substantial geographical variance, with Asia accounting for around 75% of the global incidence, mortality and 5-year prevalence (*3*).

Summary of evidence: benefits

Nasopharyngeal carcinoma

JUPITER-02 was an international, multicentre, randomized, double-blind phase III study conducted in Asian regions endemic for nasopharyngeal carcinoma. The study compared toripalimab in combination with gemcitabine and cisplatin with gemcitabine and cisplatin in 289 patients with previously untreated recurrent or metastatic nasopharyngeal cancer (*5*). Most patients in the Asian regions endemic for nasopharyngeal carcinoma have non-keratinizing histology, closely associated with the Epstein–Barr virus. Participants were randomized 1:1 to receive toripalimab 240 mg or placebo in combination with gemcitabine 1000 mg/m^2 and cisplatin 80 mg/m^2 every 3 weeks for up to six cycles, followed by toripalimab or placebo monotherapy. The primary endpoint was progression-free survival as assessed by a blinded independent review committee. Overall survival was assessed as a secondary endpoint. At the final progression-free survival analysis (8 June 2021), median follow-up was 22.1 months for the toripalimab arm and 21.4 months for the placebo arm. Median progression-free survival was 21.4 months and 8.2 months in the toripalimab and placebo arms, respectively (hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.37 to 0.73). As of the cut-off date of 18 November 2022, following a median survival follow-up of 36.0 months, 133 overall survival events were recorded, triggering the prespecified final overall survival analysis. The median overall survival was not reached in the toripalimab group and was 33.7 months in the placebo group. Toripalimab was associated with a significant improvement in overall survival compared with placebo (HR 0.63, 95% CI 0.45 to 0.89). Overall survival rates for toripalimab versus placebo groups at 1, 2 and 3 years were 90.9% versus 87.1%, 78.0% versus 65.1% and 64.5% versus 49.2%, respectively. Consistent progression-free survival treatment effects were observed across all major subgroups. The overall survival treatment effects were generally consistent across major subgroups, with the exception of patients with primary metastatic disease at baseline (HR 1.23, 95% CI 0.70 to 2.18). Treatment effects on overall survival favoured toripalimab in PD-L1 expression subgroups of < 1% (HR 0.36, 95% CI 0.4 to 0.93) and ≥ 1%

(HR 0.71, 95% CI 0.48 to 1.04). Additionally, a subgroup analysis showed benefit favouring toripalimab in patients with both low (< 2000 baseline Epstein–Barr virus DNA copy number; HR 0.76, 95% CI 0.40 to 1.46) and high (≥ 2000 baseline Epstein–Barr virus DNA copy number; HR 0.59, 95% CI 0.40 to 0.89), suggesting that toripalimab will benefit patients with keratinizing nasopharyngeal cancer in non-endemic settings for nasopharyngeal carcinoma.

POLARIS-02 was a single-arm, multicentre phase II study that evaluated the antitumour activity, safety and biomarkers of toripalimab 3 mg/kg once every 2 weeks in 190 patients in China with previously treated recurrent or metastatic nasopharyngeal carcinoma (*6*). Participants received toripalimab until disease progression, unacceptable toxicity or withdrawal of informed consent. The primary endpoint was objective response rate as determined by an independent review committee. Almost half of the participants had received at least two prior lines of systemic chemotherapy. Most participants (95.8%) had non-keratinizing nasopharyngeal carcinoma histology. One year after the last enrolment, 18 (9.5%) participants remained on treatment. Median treatment duration was 3.7 months. The objective response rate for the 190 patients was 20.5%. Median duration of response was 12.8 months, median progression-free survival was 1.9 months and median overall survival was 17.4 months. In the subgroup of participants who had received at least two prior lines of treatment ($n = 92$), the objective response rate was 23.9%, median duration of response was 21.5 months, median progression-free survival was 2.0 months and median overall survival was 15.1 months. Objective response rates in participants with PD-L1 expression > 1% and participants with negative PD-L1 expression were 27.1% and 19.4%, respectively, however, the difference was not statistically significant.

Oesophageal squamous cell carcinoma

JUPITER-06 was a randomized, double-blind, multicentre, phase III trial that compared toripalimab in combination with paclitaxel and cisplatin with paclitaxel and cisplatin in 514 Chinese patients with previously untreated advanced oesophageal squamous cell carcinoma (*7*). Patients were randomized 1:1 to receive toripalimab 240 mg or placebo in combination with paclitaxel 175 mg/kg and cisplatin 75 mg/m^2 every 3 weeks for up to six cycles followed by toripalimab or placebo monotherapy. Coprimary endpoints were progression-free survival as assessed by a blinded independent central review committee and overall survival in the intention-to-treat population. At the prespecified final analysis, median progression-free survival was 5.7 months in the toripalimab arm versus 5.5 months in the placebo arm (stratified HR for progression or death 0.58, 95% CI 0.46 to 0.74). The 1-year progression-free survival rates were 27.8% in the toripalimab arm and 6.1% in the placebo arm. Median overall survival was 17 months versus 11 months in the toripalimab and placebo arms, respectively

(stratified HR for death 0.58, 95% CI 0.43 to 0.78). In the intention-to-treat population, the objective response rate and disease control rate as assessed by the blinded independent central review committee was higher in the toripalimab arm (objective response rate 69.3% versus 52.1%; disease control rate 89.1% versus 82.1%). Treatment effects on overall survival favoured toripalimab in subgroups of patients with low and high PD-L1 expression.

A 2022 systematic review and network meta-analysis of five randomized controlled trials (3163 participants) evaluated the efficacy and safety of different PD-1 inhibitors (camrelizumab, nivolumab, pembrolizumab, sintilimab and toripalimab) in combination with chemotherapy as first-line treatment for advanced oesophageal cancer (*8*). Significant improvements in overall survival (HR 0.69, 95% CI 0.62 to 0.76), progression-free survival (HR 0.62, 95% CI 0.55 to 0.70) and objective response rate (risk ratio 1.41, 95% CI 1.23 to 1.62) were observed when a PD-1 inhibitor was added to chemotherapy. Toripalimab plus chemotherapy achieved greater overall survival benefit relative to chemotherapy alone than the other PD-1 inhibitors plus chemotherapy. Pooled subgroup analyses suggested a significant overall survival benefit associated with PD-1 inhibitor therapy in patients with PD-L1 tumour-positive score ≥ 10% (HR 0.57, 95% CI 0.46 to 0.70). Similar findings have been reported in another systematic review and meta-analysis of immune-checkpoint inhibitors for first- and later-line treatment of advanced or metastatic oesophageal squamous cell carcinoma (*9*).

Summary of evidence: harms

Treatment-related adverse events occurring in ≥ 5% of patients from the toripalimab monotherapy safety database, or the JUPITER-02 and JUPITER-06 trials of toripalimab in combination with chemotherapy were reported in the application and were unchanged from those reported in the 2023 application. Treatment-related adverse events (all grades) that occurred more frequently in the toripalimab monotherapy population than the toripalimab plus chemotherapy population include hyperbilirubinaemia, abnormal thyroid function test, abnormal creatine phosphokinase, abnormal lipids, increased amylase and proteinuria. Grade ≥ 3 hyperbilirubinaemia was reported slightly more frequently in the monotherapy group.

Additional evidence

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WHO guidelines

WHO guidelines for treatment of nasopharyngeal and oesophageal squamous cell carcinoma are not currently available.

Toripalimab in combination with gemcitabine and cisplatin is recommended in the 2025 guidelines of the United States National Comprehensive

Cancer Network guidelines for first-line treatment of recurrent, unresectable, oligometastatic or metastatic nasopharyngeal cancer (*10*).

The application reported that the 2024 guidelines of the Chinese Society of Clinical Oncology include the following recommendations for toripalimab use:

- in combination with gemcitabine and cisplatin as first-line treatment of recurrent or metastatic nasopharyngeal carcinoma, and as monotherapy for treatment-experienced patients;
- in combination with paclitaxel and cisplatin as first-line treatment of recurrent or metastatic oesophageal squamous cell carcinoma.

Costs/cost–effectiveness

Nasopharyngeal carcinoma

A 2024 analysis evaluated the cost–effectiveness of toripalimab plus chemotherapy versus chemotherapy alone in American patients with recurrent or metastatic nasopharyngeal carcinoma from the United States payer perspective (*11*). Compared with chemotherapy, toripalimab plus chemotherapy was associated with an incremental cost–effectiveness ratio of 74 004 United States dollars (US$) per quality-adjusted life year (QALY), which is lower than the willingness-to-pay threshold of US$ 150 000 per QALY.

A 2024 economic simulation study estimated the cost–efficiency of toripalimab plus chemotherapy versus pembrolizumab plus chemotherapy for the treatment of recurrent or metastatic nasopharyngeal carcinoma for an assumed 1207 incident cases in the United States in 2024 (*12*). The simulation used wholesale acquisition costs and an assumed price for toripalimab of 80% of the average sales price of pembrolizumab. The study found that assuming 90% of new cases of recurrent or metastatic nasopharyngeal cancer were treated with toripalimab instead of pembrolizumab, savings realized over 1 year would be US$ 43.5 million, which would be sufficient to purchase an additional 4717 doses on a budget-neutral basis.

A 2024 modelling study estimated the budget impact of toripalimab versus pembrolizumab in the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma in the United States (*13*). The model used a 3-year time horizon and assumed a market share split (toripalimab/pembrolizumab) of 60/40 in year 1 and increasing to 80/20 in years 2 and 3. The study used published wholesale acquisition costs and average sales prices and considered a treatment mix without versus with toripalimab in the eligible incident US population. It was estimated that savings of about US$ 180 million over 3 years could be achieved by using a toripalimab-containing regimen over a pembrolizumab-containing regimen.

A 2023 network meta-analysis and cost–effectiveness analysis evaluated the cost–effectiveness of toripalimab, camrelizumab and tislelizumab, all plus

chemotherapy, and chemotherapy alone as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma from a Chinese payer perspective (*14*). Compared with chemotherapy alone, toripalimab, camrelizumab and tislelizumab added to chemotherapy were associated with incremental cost–utility ratios of US$ 25 576, US$ 31 370 and US$ 31 729 per QALY, respectively. All were found to be cost-effective at a willingness-to-pay threshold of US$ 38 029 per QALY. In pairwise comparisons between the PD-1 inhibitors, toripalimab with chemotherapy was the most cost-effective option.

Oesophageal squamous cell carcinoma

A 2023 analysis evaluated the cost–effectiveness of PD-1 inhibitors in combination with chemotherapy as first-line therapy for advanced oesophageal squamous cell carcinoma from the Chinese health-care system perspective (*15*). In the base-case analysis over a 10-year time horizon, compared with chemotherapy alone, toripalimab, sintilimab and camrelizumab added to chemotherapy were associated with incremental cost–effectiveness ratios of US$ 14 047, US$ 18 622 and US$ 29 771 per QALY, respectively, which are lower than a willingness-to-pay threshold of US$ 38 351 per QALY. In contrast, other PD-1 inhibitors were not cost-effective, with incremental cost–effectiveness ratios versus chemotherapy alone of US$ 170 911, US$ 211 350 and US$ 400 769 per QALY for serplulimab, pembrolizumab and nivolumab plus chemotherapy, respectively.

Availability

Toripalimab has regulatory approval for use in the treatment of metastatic or recurrent locally advanced nasopharyngeal carcinoma in China, Europe, India and the United States. Regulatory approval for toripalimab in the treatment of oesophageal squamous cell carcinoma has, to date, only been granted in China. Regulatory applications have been submitted in Australia, Chile, Jordan, Singapore, South Africa and the United Kingdom of Great Britain and Northern Ireland.

Other considerations

The EML cancer experts group reviewed the application but were unable to reach consensus on whether to support the inclusion of toripalimab on the EML for nasopharyngeal cancer.

The group did not support the inclusion of toripalimab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma. The group judged that the reported gains in overall survival were moderate in size and offset by the unclear role of PD-L1 expression as a predictive biomarker. Long-term data on the class of immune checkpoint inhibitors were lacking.

Committee recommendations

The Expert Committee recognized the significant public health burden of oesophageal squamous cell carcinoma and nasopharyngeal carcinoma, particularly in Asia where the diseases are considered endemic with disproportionately high incidence, prevalence and mortality. The Asian region accounts for about 75% and 85% of the global burden of oesophageal squamous cell carcinoma and nasopharyngeal carcinoma, respectively.

In nasopharyngeal carcinoma, the Committee considered evidence from toripalimab clinical trials that showed promising overall survival gains, surpassing the EML threshold of 4–6 months, for toripalimab in combination with chemotherapy over chemotherapy alone in the first-line setting. The magnitude of overall survival benefit in the second-line setting was more limited, However, the Committee also noted that trials of other immune checkpoint inhibitors in treatment of nasopharyngeal carcinoma (e.g. camrelizumab and tislelizumab) are ongoing. The Committee considered it would be of interest to evaluate the benefits of these medicines as a class in treatment of nasopharyngeal carcinoma, particularly in the first-line setting.

The Expert Committee therefore did not recommend the inclusion of toripalimab on the EML for the treatment of nasopharyngeal carcinoma at this time. The Committee underscored that more mature additional data for all immune checkpoint inhibitors approved for nasopharyngeal carcinoma, especially on overall survival and quality of life, will be pivotal to inform judgements on whether to include toripalimab on the EML in the future.

In oesophageal squamous cell carcinoma, the Committee considered evidence from the JUPITER-06 trial that showed an overall survival benefit of around 6 months for toripalimab plus chemotherapy compared with chemotherapy alone in the first-line setting. As regards the comparative effectiveness of toripalimab and other immune checkpoint inhibitors for oesophageal squamous cell carcinoma in the first-line setting, the Committee found the magnitudes of effect on overall survival to be relatively consistent at about 6 months overall survival gain compared with chemotherapy, which the Committee judged to be moderate. In each case, treatment was in combination with chemotherapy. The Committee considered that this finding suggested a class effect and the potential for medicines within the class to be considered as therapeutic alternatives. Data for toripalimab in the second-line setting were not available.

The Committee agreed with the EML cancer expert group that the role of PD-L1 expression as a predictive biomarker for benefit was unclear. The Committee also noted the lack of long-term survival data for the class of immune checkpoint inhibitors. The Committee noted the potential for increased harm in patients with a poor performance status and poorer prognosis at baseline, a population that is relatively underrepresented in trials.

The Committee noted that toripalimab was likely to be the more cost-effective option compared with pembrolizumab, nivolumab, nivolumab plus ipilimumab, and tislelizumab. However, the Committee considered that the cost of treatment may still have a substantial budget impact, particularly in resource-constrained settings.

Based on these considerations, the Expert Committee did not recommend the inclusion of toripalimab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma in the first- or later-line setting. In terms of the class, the Committee considered that ongoing trials and determination of the role of PD-L1 expression as a predictive biomarker would be informative for future consideration of these medicines for this indication.

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8.2.5 Supportive medicines

Erythropoiesis-stimulating agents – new indication – EML and EMLc

Erythropoiesis-stimulating agents	
Epoetin alfa	**ATC code: B03XA01**
Epoetin beta	**ATC code: B03XA03**
Darbepoetin alfa	**ATC code: B03XA02**

Proposal

Inclusion of erythropoiesis-stimulating agents (epoetin alfa, epoetin beta and darbepoetin alfa) on the complementary list of the EML and EMLc for the new indication of treatment of chemotherapy-induced anaemia in adults and children with non-myeloid malignancies receiving myelosuppressive chemotherapy.

Applicant

Resonance, Inc., Memphis, TN, United States of America

WHO technical department

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team supported the inclusion of erythropoiesis-stimulating agents on the Model Lists for chemotherapy-induced anaemia in a carefully defined subset of patients who were adhering to established supportive care standards and were under the close supervision of trained health-care professionals to ensure safe and effective use. The technical team noted that although data do not support a survival benefit from these medicines, their use may be justified in selected patients to reduce red blood cell transfusions and improve quality of life.

EML/EMLc

EML and EMLc

Section

8.2.5 Supportive medicines

Dose form(s) & strengths(s)

Epoetin alfa

Injection: 2000 IU/mL, 3000 IU/mL, 4000 IU/mL, 10 000 IU/mL, 40 000 IU/mL in single-dose vial; 20 000 IU/mL, 20 000 IU/2 mL in multiple-dose vial

Epoetin beta

Injection: 500 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU, 6000 IU, 10 000 IU, 20 000 IU, 30 000 IU in prefilled syringe

Darbepoetin alfa

Injection: 10 microgram, 15 microgram, 20 microgram, 30 microgram, 40 microgram, 50 microgram, 6 microgram, 80 microgram, 100 microgram, 130 microgram, 150 microgram, 300 microgram, 500 microgram in prefilled pen or prefilled syringe; 25 microgram, 40 microgram, 60 microgram, 100 microgram, 200 microgram, 300 microgram in vial

Core/complementary

Complementary

Individual/square box listing

Square box listing for erythropoiesis-stimulating agents as a therapeutic group, specifying epoetin alfa, epoetin beta and darbepoetin alfa (including quality-assured biosimilars) as therapeutic alternatives.

Background

Erythropoiesis-stimulating agents have not previously been evaluated for inclusion on the Model Lists for the proposed indication.

Erythropoiesis-stimulating agents (including biosimilars) have been included on the Model Lists since 2017 for the treatment of adults and children with anaemia of chronic kidney disease (*1*).

Public health relevance

Anaemia is a condition characterized by deficiency of red blood cells or haemoglobin, which diminishes the capacity of the blood to carry oxygen necessary for tissues and organs (*2*). It is a common adverse effect of myelosuppressive chemotherapy and affects around 80% of patients undergoing treatment (*2*, *3*). Symptoms include fatigue, drowsiness, depression, dyspnoea, tachycardia and dizziness. Chemotherapy-induced anaemia can have a negative effect on quality of life, and it is associated with substantial economic burden and medical costs (*4*–*6*).

Chemotherapy-induced anaemia may be treated using red blood cell transfusions. In low- and middle-income countries, availability of high-quality blood transfusion services for anaemia management may be limited. The WHO Global Status Report on Blood Safety and Availability 2021 reported lower rates of whole blood donations per 1000 population in low- and middle-income countries, as well as higher rates of blood donations with positive/reactive results for transfusion-transmissible infections on screening tests (*7*).

Summary of evidence: benefits

The application did not report having conducted a systematic search of the literature and did not provide an adequate summary of the evidence to support the comparative effectiveness of erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia.

Summary of evidence: harms

The application did not report having conducted a systematic search of the literature and did not provide an adequate summary of the evidence to support the comparative safety of erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia.

The application stated that the use of erythropoiesis-stimulating agents has been associated with increased risk of thromboembolic events (particularly when haemoglobin levels are higher than 12 g/dL) and increased risk of tumour progression (*8*, *9*).

Additional evidence

The following evidence was identified during the application review period.

A 2012 Cochrane systematic review of 91 randomized controlled trials (20 102 participants) assessed the effects of erythropoiesis-stimulating agents for the prevention or treatment of anaemia in cancer patients (*10*). Only one of the trials evaluated erythropoiesis-stimulating agents in children. The review found that the use of erythropoietin or darbepoetin significantly reduced the risk of requiring red blood cell transfusions (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.62 to 0.68; 70 trials, 15 935 participants). Additionally, participants receiving erythropoiesis-stimulating agents received fewer units of blood if transfused than controls (mean difference (MD) −0.98 units, 95% CI −1.17 to −0.78; 19 trials, 4715 participants). More participants receiving erythropoiesis-stimulating agents achieved a haematological response – defined as the proportion of patients with an increase in haemoglobin level of 2 g/dL or more, or an increase in haematocrit of 6% points or more – (RR 3.93, 95% CI 3.10 to 3.71; 31 trials, 6413 participants). There was low-certainty evidence that erythropoiesis-stimulating agents may improve quality of life. There was high-certainty evidence that erythropoiesis-stimulating agents may decrease overall survival (hazard ratio (HR) 1.05, 95% CI 1.00 to 1.11; 78 trials, 19 003 participants) and increase the risk of death (HR 1.17, 95% CI 1.06 to 1.29; 70 trials, 15 935 participants). Mortality risk was higher in patients with higher baseline haemoglobin levels > 12 g/dL (HR 1.37, 95% CI 1.12 to 1.68; 13 trials, 3923 participants). Erythropoiesis-stimulating agents were also associated with an increased risk of thromboembolic complications (RR 1.52, 95% CI 1.34 to 1.74, 57 trials, 15 498 participants), hypertension (RR 1.30, 95% CI 1.08 to

1.56; 31 trials 7228 participants) and thrombocytopenia/haemorrhage (RR 1.21, 95% CI 1.04 to 1.42, 21 trials, 4507 participants).

A 2009 meta-analysis of 53 randomized controlled trials (13 933 participants) evaluated mortality risk of recombinant human erythropoiesis-stimulating agents in patients with cancer (*11*). In 38/53 (72%) trials, patients received chemotherapy, while in 5/53 (9%) trials, patient received radio-chemotherapy. The remaining trials did not include the use of chemotherapy. Median follow-up was 3.7 months and 3.9 months in the erythropoiesis-stimulating agents and control groups, respectively. Across all trials, treatment with erythropoiesis-stimulating agents was associated with an increased mortality risk (HR 1.17, 95% CI 1.06 to 1.30). Considering only the chemotherapy trials, the mortality risk remained increased, albeit slightly lower (HR 1.10, 95% CI 0.98 to 1.24).

WHO guidelines

WHO guidelines for the treatment of chemotherapy-induced anaemia are not available.

In clinical guidelines from various oncology and haematology organizations, recommendations for the use of erythropoiesis-stimulating agents include: to consider using only in patients with symptomatic chemotherapy-induced anaemia when haemoglobin levels are lower than 10 g/dL; cautioning against use in patients receiving chemotherapy with curative intent; discussing the potential risks and benefits with patients and obtaining informed consent; regular monitoring; and using the lowest effective dose to achieve target haemoglobin levels.

Costs/cost–effectiveness

The application stated that the cost of erythropoiesis-stimulating agents varies across regions. Prices can be higher in low- and middle-income countries than in high-income countries due to import and supply chain costs. The introduction of biosimilars has helped to reduce costs (*12*).

The application identified several cost–effectiveness analyses for erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anaemia (*13*–*18*), but highlighted their limitations as they were all conducted in high-income countries only and were not published recently.

Availability

Erythropoiesis-stimulating agents, including biosimilars, are widely available in high-income countries but may be less widely available and accessible in resource-constrained countries.

Other considerations

–

Committee recommendations

The Expert Committee acknowledged that anaemia is a relatively common complication of chemotherapy treatment and is associated with reduced quality of life and functional capacity for patients.

The Committee noted that judicious use of erythropoiesis-stimulating agents in patients with chemotherapy-induced anaemia has been shown to improve haemoglobin levels, may reduce transfusion requirements and may be associated with improvements in quality of life. However, their use has not been shown to improve overall survival, with some studies reporting inferior survival and worse cancer outcomes as these medicines might stimulate tumour growth directly or affect the tumour microenvironment, limiting effective immune responses. The Committee also noted that guidelines from professional societies (e.g. the American Society of Clinical Oncology and the European Society of Medical Oncology) recommend careful patient selection, informed consent about risks and conservative dosing – factors that are important limitations in terms of feasibility in the use of this class of medicines.

Therefore, the Expert Committee did not recommend the expansion of the indications for erythropoiesis-stimulating agents on the EML and EMLc to include supportive management of chemotherapy-induced anaemia, based on evidence of a potentially unfavourable long-term benefit-to-harm profile.

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Section 10: Medicines affecting the blood

Changes to Subsection 10.3

The Expert Committee endorsed changes to Subsection 10.3 of the Model Lists made by the Secretariat, incorporating the suggestions made by the WHO Department of Maternal, Newborn, Child and Adolescent Health, and Ageing: to title the section "Medicines for haemoglobinopathies" and to transfer the listing of hydroxyurea (hydroxycarbamide) from the complementary to the core list.

10.2 Medicines affecting coagulation

Emicizumab – addition – EML and EMLc

Emicizumab **ATC code: B02BX06**

Proposal

Addition of emicizumab to the core list of the EML and EMLc for the treatment of people with:

- all severities of haemophilia A and inhibitors to factor VIII (FVIII); and
- severe haemophilia A without inhibitors to FVIII.

Applicant

World Federation of Hemophilia

WHO technical department

The blood and other products of human origin team within the Department of Health Products, Policy and Standards reviewed and provided comments on the application. The technical team supported the inclusion of emicizumab on the EML and EMLc based on evidence of favourable efficacy and cost–effectiveness.

EML/EMLc

EML and EMLc

Section

10.2 Medicines affecting coagulation

Dose form(s) & strengths(s)

Injection: 30 mg/mL, 150 mg/mL in vial

Core/complementary

Core

Individual/square box listing

Individual

Background

Emicizumab has not previously been evaluated for inclusion on the Model Lists for treatment of people with haemophilia A.

The Model Lists currently include plasma-derived FVIII and desmopressin for use in the treatment of haemophilia A. Pathogen-reduced cryoprecipitate (with non-pathogen-reduced cryoprecipitate as a therapeutic alternative) is also listed for use in the treatment of haemophilia A as an alternative to FVIII in circumstances when plasma-derived clotting factors are not available or affordable.

Public health relevance

The public health relevance of treatments for haemophilia A is well established.

The prevalence at birth per 100 000 males is estimated to be 24.6 cases for all severities of haemophilia A, 9.5 cases for severe haemophilia A, 5.0 cases for all severities of haemophilia B, and 1.5 cases for severe haemophilia B (*1*). According to estimates on the prevalence at birth and based on the world population in 2024, the expected number of people born with haemophilia is about 1.2 million, including 451 000 with severe disease.

The prevalence of haemophilia at birth is similar worldwide; however, survival to adulthood, especially in patients with severe disease, is lower in low- and middle-income countries with restricted access to efficacious coagulation therapies (*1*).

Patients treated with exogenous factor VIII replacement can develop inhibitors (alloantibodies) against FVIII, rendering it ineffective. New FVIII inhibitors occur in approximately 30% of people with haemophilia A who receive coagulation factor concentrates. Most patients develop an inhibitor within a median of 9–12 exposure days to FVIII. The overall inhibitor prevalence is reported to be 5–7% (all patients, all severities), but is higher in patients with severe disease (12–13%) (*2*).

Summary of evidence: benefits

Systematic reviews and meta-analyses

Non-clotting factor therapies to prevent bleeds in people with congenital haemophilia A or B

A 2024 Cochrane systematic review of six randomized controlled trials (397 males aged 12–75 years) evaluated non-clotting factor therapies (concizumab, emicizumab and fitusiran) versus clotting factor therapies, bypassing agents, placebo or no treatment in the prevention of bleeding and bleeding-related complications in people with congenital haemophilia A or B (*3*).

For the comparison of emicizumab prophylaxis (3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) versus on-demand therapy in people with inhibitors, the review found moderate-certainty evidence from one trial (HAVEN 1, 53 participants) that emicizumab reduced annualized bleeding rates for all bleeds (mean difference (MD) −22.80, 95% confidence interval (CI) −37.39 to −8.21), all treated bleeds (MD −20.40, 95% CI −35.19 to −5.61) and annualized spontaneous bleeds (MD −15.50, 95% CI −24.06 to −6.94) compared with on-demand therapy. Emicizumab did not significantly reduce annualized joint bleeding rates (MD −5.90, 95% CI −15.42 to 3.62) or annualized target joint bleeding rates (MD −2.90, 95% CI −8.61 to 2.81) compared with on-demand therapy. Emicizumab was associated with a significant increase in the proportion of participants with no bleeds (risk ratio (RR) 11.30, 95% CI 1.66 to 77.30). Quality of life outcomes measured using the Haemophilia Quality of Life Questionnaire for Adults showed low-certainty evidence from one randomized controlled trial (40 participants) of improvements in total score (MD −13.20, 95% CI −20.84 to −5.56) and physical health score (MD −20.20, 95% CI −32.38 to −8.02) (*3*).

For the comparison of emicizumab 1.5 mg/kg weekly prophylaxis versus on-demand therapy in people without inhibitors (one randomized controlled trial (HAVEN 3), 54 participants), there was moderate-certainty evidence that emicizumab reduced annualized bleeding rates for all bleeds (MD −45.10, 95% CI −63.44 to −26.76), for treated bleeds (MD −36.70, 95% CI −60.53 to −12.87) and annualized joint bleeding rate (MD −25.40, 95% CI −45.23 to −5.57). For the comparison of emicizumab prophylaxis (3 mg/kg bi-weekly) versus on-demand therapy in people without inhibitors (one randomized controlled trial, 53 participants), there was moderate-certainty evidence that emicizumab also reduced annualized bleeding rates for all bleeds (MD −45.00, 95% CI −63.19 to −26.81), for treated bleeds (MD −36.90, 95% CI −60.67 to −13.13) and for annualized joint bleeding rate (MD −25.60, 95% CI −45.40 to −5.80). No differences were seen between emicizumab (either dose) or on-demand therapy for the annualized target joint bleeding rate. There was moderate-certainty evidence that bi-weekly emicizumab reduced the annualized spontaneous joint bleeding rate compared with on-demand therapy (MD −15.30, 95% CI −30.46 to −0.14) (*3*).

Another 2024 systematic review and meta-analysis of five publications (one randomized controlled trial, two non-randomized controlled trials and two cohort studies; 556 participants) compared bleeding endpoints between prophylaxis with emicizumab and bypassing agents (*4*). The emicizumab treatment regimen investigated was 3 mg/kg weekly for 1 month (all publications) followed by 1.5 mg/kg weekly (four publications). Annualized bleeding rates for treated bleeds was the only common parameter reported in all publications. Results of the meta-analysis for all publications found that emicizumab prophylaxis was

associated with a significant reduction in annualized bleeding rates for treated bleeds (standard mean deviation (SMD) −1.58, 95% CI −2.50 to −0.66). The authors highlighted the need to consider these results in the context of small population size and potential risk of bias in the studies.

A 2023 systematic review of 11 publications from 10 studies (two randomized controlled trials, three non-randomized trials, five observational studies, 858 participants) evaluated the efficacy/effectiveness and safety of emicizumab prophylaxis compared with prophylaxis with FVIII or bypassing agents in patients with haemophilia A without and with inhibitors (5). In patients without inhibitors, a significant reduction in annualized bleeding rates was observed for emicizumab compared with FVIII prophylaxis (SMD −0.6, 95% CI −1.0 to −0.2; $P = 0.0002$; seven publications, 208 participants). Subgroup analyses showed significant reductions favouring emicizumab from both interventional (SMD −0.6, 95% CI −1.0 to −0.3; $P = 0.0007$) and observational (SMD −0.7, 95% CI −1.4 to 0.1; $P = 0.07$) studies. No significant reduction was observed between treatment groups for annualized bleeding rates for spontaneous treated bleeds or traumatic treated bleeds. The certainty of the evidence for these outcomes was very low.

In patients with inhibitors, a significant reduction in annualized bleeding rates was observed for emicizumab compared with FVIII prophylaxis (SMD −1.7, 95% CI −2.4 to −0.9; $P < 0.00001$; seven publications, 97 participants). Subgroup analyses showed significant reductions favouring emicizumab from both interventional (SMD −1.6, 95% CI −3.0 to −0.1; $P = 0.03$) and observational (SMD −1.9, 95% CI −2.5 to −1.3; $P < 0.00001$) studies. The certainty of the evidence for these outcomes was very low. The review was not able to measure the effect estimates for annualized bleeding rates for spontaneous or traumatic treated bleeds (5).

Randomized and non-randomized trials

Studies in people with haemophilia A of any age or severity and with inhibitors to FVIII

The HAVEN 1 trial was a phase III, open-label, multicentre, randomized trial that compared emicizumab prophylaxis with no prophylaxis in 109 patients with haemophilia A with inhibitors aged 12 years and older (6). Participants were randomized in a 2:1 ratio to receive emicizumab 3 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly (group A, 35 participants), or no prophylaxis (group B, 18 participants). Participants who had previously received prophylactic treatment with bypassing agents received emicizumab prophylaxis in group C (49 participants). The primary endpoint was difference in the annualized bleeding rates at 24 weeks between treatment groups A and B. The reported annualized bleeding rates were 2.9 events (95% CI 1.7 to 5.0) for emicizumab compared with 23.3 events (95% CI 12.3 to 43.9) for no prophylaxis, representing an

87% difference that significantly favoured emicizumab (risk ratio (RR 0.13; $P < 0.001$). Zero bleeding events were reported in 22/35 (63%) and 1/18 (6%) of patients randomized to receive emicizumab and no prophylaxis, respectively. Significant differences in favour of emicizumab prophylaxis were also observed in all secondary bleeding-related endpoints. Among the 24 participants who had previously received prophylactic treatment with bypassing agents, emicizumab prophylaxis resulted in a 79% reduction in annualized bleeding rates ($P < 0.001$).

Health related outcomes from HAVEN 1 were reported in a subsequent study (*7*). At week 25, significant differences were seen favouring emicizumab in adjusted mean scores on the Haemophilia Quality of Life Questionnaire for Adults (14.0, 95% CI 5.6 to 22.5; $P = 0.002$) and physical health (21.6, 95% CI 7.9 to 35.2; $P = 0.003$). The mean proportions of missed work days and days hospitalized were lower in patients treated with emicizumab compared with those who received no prophylaxis.

The HAVEN 2 trial was a phase III, open-label non-randomized trial that investigated emicizumab prophylaxis in children aged < 12 years (85 participants) and ≥ 12 years (three participants) with haemophilia A with inhibitors (*8*). Participants received emicizumab: 1.5 mg/kg weekly (group A, 65 participants), 3 mg/kg bi-weekly every 2 weeks (group B, 10 participants) or 6 mg/kg 4-weekly (group C, 10 participants). The annualized bleeding rates for treated bleeds for groups A, B and C were 0.3 (95% CI 0.17 to 0.50), 0.2 (95% CI 0.03 to 1.72) and 2.2 (95% CI 0.69 to 6.81), respectively. The proportions of patients experiencing zero bleeds were 77% (group A), 90% (group B) and 60% (group C). An intraindividual comparison of 15 participants who previously took bypassing agent prophylaxis showed that emicizumab prophylaxis reduced the annualized bleeding rates by 99% (95% CI 97.4 to 99.4).

Health-related outcomes from HAVEN 2 were reported in a subsequent study (*9*). Health-related quality of life was assessed using the Haemophilia-Specific Quality of Life Index (Haemo-QoL SF) in 11 children and the Adapted Inhibitor-specific Quality of Life in caregivers. Mean baseline scores across most of the domains on both measures indicated functional impairments. Over the study period (25 weeks), mean scores for physical health or other domains reported by children or caregivers did not change substantially.

The HAVEN 4 trial was a phase III, multicentre, non-randomized, open-label, two-stage trial that investigated the efficacy, safety and pharmacokinetics of emicizumab 6 mg/kg 4-weekly for 24 weeks in 41 adults and adolescents with haemophilia A with ($n = 5$) and without ($n = 36$) inhibitors (*10*). The efficacy endpoint was adequate bleed prevention reported as annualized bleed rates for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds. Health-related quality of life was evaluated using the Haemophilia Quality of Life Questionnaire for Adults and Haemo-QoL-SF. The

annualized bleeding rates for treated bleeds was 2.4 (95% CI 1.4 to 4.3). No treated bleeds were reported in 23/41 participants, while 37/41 participants reported zero to three treated bleeds. The annualized bleeding rates were 4.5 (95% CI 3.1 to 6.6) for all bleeds, 0.6 (95% CI 0.3 to 1.5) for treated spontaneous bleeds, 1.7 (0.8 to 3.7) for treated joint bleeds, and 1.0 (95% CI 0.3 to 3.3) for treated target joint bleeds. Improvements in the Haemophilia Quality of Life Questionnaire for Adults Physical Health Score from baseline to week 25 were also reported.

The STASEY trial was a phase IIIb, multicentre single-arm study that evaluated long-term efficacy and safety of emicizumab 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly in 195 patients aged 12 years and older with haemophilia A with inhibitors (*11*). The annualized bleeding rate for treated bleeds was 0.5 (95% CI 0.27 to 0.89) with 82.6% of participants experiencing zero treated bleeds. The annualized bleeding rates for all bleeds was 1.1 (95% CI 0.80 to 1.47), with 64.9% of patients experiencing zero bleeds.

A 2023 post-marketing study in the United Kingdom evaluated bleeding outcomes in patients with haemophilia A with inhibitors using data for 117 patients from a national registry and patient-reported Haemtrack data over 3 years (January 2018 to September 2021) (*12*). Of the 117 patients, 106 had severe haemophilia and 11 had non-severe disease. Four patients were younger than 2 years. Over a mean emicizumab treatment duration of 42 months, the mean annualized bleeding rate was 0.32 events (95% CI 0.18 to 0.39). A within-person comparison of 74 patients showed an 89% reduction in annualized bleeding rates after switching to emicizumab (from no treatment, plasma-derived or recombinant FVIII, activated prothrombin complex concentrate or multiple treatments) and an increase in the zero-treated bleed rate from 45% to 88% ($P < 0.01$). In a subgroup of 37 patients who switched from other treatments to emicizumab, over a median 25 months of follow-up, total haemophilia joint health scores improved from baseline in 39% of patients, remained stable in 36% and deteriorated in 25%. The within-person change in total haemophilia joint health scores was statistically significant but did not meet the threshold for clinical significance.

Studies in people with severe haemophilia A without inhibitors to FVIII

The HAVEN 3 trial was an open-label, multicentre randomized trial that evaluated emicizumab prophylaxis in 152 participants aged 12 years or older with severe haemophilia A without inhibitors (*13*). Participants were randomized in a 2:2:1 ratio to receive emicizumab 1.5 mg/kg weekly (group A, $n = 36$), emicizumab 3 mg/kg bi-weekly (group B, $n = 35$) or no prophylaxis (group C, $n = 18$). Participants who had previously been receiving FVIII prophylaxis were given emicizumab 1.5 mg/kg weekly (group D, $n = 63$). The primary endpoint was the difference in the rate of treated bleeding events over a period of at

least 24 weeks between treatment groups. The annualized bleeding rates were 1.5 (95% CI 0.9 to 2.5), 1.3 (95% CI 0.8 to 2.3) and 38.2 (95% CI 22.9 to 63.8) in groups A, B and C, respectively. Compared with group C, the bleeding rates were significantly lower in both group A (rate ratio (RR) 0.04, 95% CI 0.02 to 0.08; $P < 0.001$) and group B (RR 0.03, 95% CI 0.02 to 0.07; $P < 0.001$). The percentages of participants with zero bleeding events was 56% (95% CI 38% to 72%) in group A, 60% (95% CI 42% to 76%) in group B, and 0% (95% CI 0% to 18%) in group C. Intraindividual comparison of 48 participants in group D showed a significantly lower annualized bleeding rate favouring emicizumab over FVIII prophylaxis (RR 0.32, 95% CI 0.20 to 0.51; $P < 0.001$).

A 2022 study evaluated the effect of emicizumab prophylaxis on bone/joint health in 151 participants with haemophilia A without inhibitors from the HAVEN 3 study (*14*). Haemophilia joint health scores were evaluated at baseline and weeks 49 and 97 in patients receiving emicizumab ($n = 134$), and at baseline and weeks 49, 73 and 97 in patients who switched to emicizumab after 24 weeks of no prophylaxis ($n = 17$). At week 49, the mean improvement in total haemophilia joint health score from baseline for all participants was −1.86 (95% CI −3.53 to −0.20). Among participants with at least one target joint at study entry ($n = 71$), the mean improvement in haemophilia joint health total score at week 49 was −2.28 (95% CI −4.15 to −0.42) and the mean improvement in the haemophilia joint health score joint-specific domain was −2.13 (95% CI −3.96 to −0.29). Changes from baseline were maintained through week 97 in this patient group. In participants aged 12–39 years ($n = 67$) regardless of target joint status or previous treatment regimen, the mean improvement in haemophilia joint health total score was −3.22 (95% CI−5.40 to −1.04) and the mean improvement in haemophilia joint health score joint-specific domain was −3.04 (95% CI −5.12 to −0.97). Changes from baseline were maintained through week 97 in this patient group. A change of ≥ 4 for total haemophilia joint health scores and of ≥ 2 for haemophilia joint health score joint-specific domain is considered clinically relevant.

A 2024 study evaluated the long-term outcomes of emicizumab in 191 patients with haemophilia A without inhibitors from the HAVEN 3 and HAVEN 4 studies (*15*). Across the two studies, the median duration of emicizumab exposure was 248.1 weeks (range 6.1–287.1 weeks). The mean annualized bleeding rates for treated bleeds were 2.0 (95% CI 0.23 to 7.15) for weeks 1 to 24 and 0.9 (95% CI 0.01 to 5.28) by weeks 217 to 240.

The HAVEN 5 trial was a phase III, open-label, randomized study of emicizumab in 70 participants with severe haemophilia A without inhibitors across the Asia-Pacific region (China, Malaysia and Thailand) (*16*). Participants were randomized in a 2:2:1 ratio to receive emicizumab 1.5 mg/kg weekly (group A, $n = 29$), emicizumab 6 mg/kg 4-weekly (group B, $n = 27$) or no prophylaxis (group C, $n = 14$). For the primary efficacy endpoint of annualized bleeding rates,

after at least 24 weeks of study treatment, the annualized bleeding rates were 1.0 (95% CI 0.53 to 1.85), 1.0 (95% CI 0.50 to 1.84) and 27.0 (95% CI 13.29 to 54.91) in groups A, B and C, respectively. Significant reductions in annualized bleeding rates were observed for both emicizumab-treatment groups compared to no prophylaxis (RR 0.04; $P < 0.0001$).

Other studies in people with haemophilia A with and without inhibitors to FVIII

The HAVEN 7 trial is an ongoing phase IIIb, multicentre, open label, single-arm trial of emicizumab prophylaxis 3 mg/kg/week for 4 weeks followed by 3 mg/kg bi-weekly for 52 weeks, followed by long-term follow-up in 55 male infants aged ≤ 12 months with severe haemophilia A without inhibitors (*17*). Following a median duration of 101.9 weeks, the reported annualized bleeding rates were 2.0 (95% CI 1.49 to 2.66) for all bleeds, 0.4 (95% CI, 0.30 to 0.63) for treated bleeds, 0.0 (95% CI, 0.01 to 0.09) for treated joint bleeds and 0.1 (95% CI, 0.02 to 0.12) for treated muscle bleeds. Zero-treated bleeds were reported in 54.5% of participants. A total of 207 bleeds were reported in 46 patients, most of which (87.9%) were traumatic.

A 2021 study evaluated long-term efficacy outcomes of emicizumab prophylaxis in 400 patients with haemophilia A with or without inhibitors using pooled data from long-term follow-up of the HAVEN 1-4 trials (*18*). Across a median efficacy period of 120.4 weeks, the annualized bleeding rates for treated bleeds was 1.4 (95% CI 1.1 to 1.7) and for all bleeds was 2.6 (95% CI 2.2 to 3.1). In an analysis of 24-week treatment intervals, annualized bleeding rates for treated bleeds declined from 1.9 (95% CI 0.2 to 7.1) for weeks 1–24 ($n = 391$) to 0.8 (95% CI 0.0 to 5.2) for weeks 25–48 ($n = 374$), then remained stable to weeks 121–144 (0.4, 95% CI 0.0 to 5.0). The proportion of participants with zero bleeds increased from 70.8% for weeks 1–24 to 82.4% for weeks 121–144. The proportion of participants with three or fewer treated bleeds and no treated target joint bleeds at weeks 121–144 were 97.6% and 94.1%, respectively.

A 2022 study investigated surgical outcomes in people with haemophilia A with and without inhibitors receiving emicizumab prophylaxis using pooled data from the HAVEN 1–4 trials (*19*). A total of 233 surgeries (215 minor, 18 major) were carried out during these trials. The median emicizumab exposure before surgery was 278.0 days (interquartile range (IQR) 177.0 to 431.0 days). About two thirds (141/215, 65.6%) of the minor surgeries were managed without additional prophylactic factor concentrate, with most of these (121/141, 85.8%) not associated with a postoperative bleed. Of the major surgeries, most (15/18, 83.3%) were managed with additional prophylactic factor concentrate, with most (12/15, 80.0%) not associated with intraoperative or postoperative bleeds.

A 2021 prospective study of longitudinal real-world data evaluated the efficacy and safety of emicizumab prophylaxis in 107 patients (including

58 children) with severe haemophilia A with and without inhibitors (*20*). Participants were followed for a median of 67 weeks. Zero bleeds were reported in 53/107 (49.5%) participants.

A 2024 study evaluated data from the multicentre, prospective observational PedNet Registry for children with haemophilia A and ≥ 50 FVIII exposures or inhibitors receiving prophylactic emicizumab (*21*). A total of 177 patients started emicizumab at a median of 8.6 years (IQR 4.8 to 13.1 years); 64% had no FVIII inhibitors. The follow-up period before emicizumab was 1.7 years (IQR 1.2 to 1.9 years) and during prophylaxis with emicizumab was 1.3 years (IQR 0.9 to 2.1 years). In participants without inhibitors, the mean annualized bleeding rate was significantly reduced after starting emicizumab from 2.41 to 1.11 (incidence rate ratio (IRR) 0.47, 95% CI 0.35 to 0.63; $P < 0.001$), as was the mean annualized joint bleeding rate from 0.74 to 0.31 (IRR 0.43, 95% CI 0.26 to 0.69; $P < 0.001$). In participants with inhibitors, reductions in the annualized bleeding rates were greater: mean annualized bleeding rate reduced from 5.08 to 0.75 (IRR 0.15, 95% CI 0.10 to 0.21; $P < 0.001$) and mean annualized bleeding joint rate reduced from 1.90 to 0.34 (IRR 0.17, 95% CI 0.10 to 0.28; $P < 0.001$)

A prospective study in Côte d'Ivoire evaluated the effect of emicizumab prophylaxis on bleeds, clotting factor concentrate consumption, quality of life and patient/parent satisfaction in 33 boys (2–13 years) with severe haemophilia A with and without inhibitors (*22*). In this setting, access to clotting factor concentrates is limited to humanitarian aid. Twelve months after initiation of emicizumab, significant reductions were reported in mean (standard error) annualized bleeding rate (−7.3 (0.8); $P < 0.0001$) and annualized spontaneous joint bleeding rate (−3.3 (0.6); $P < 0.0001$). The proportion of boys with no spontaneous joint bleeds increased from 18% to 100%. Three boys (without inhibitors) required a single FVIII infusion following a traumatic bleed. At 6 months, health-related quality of life measures significantly improved and perception of treatment efficacy was positively rated by children and parents.

Summary of evidence: harms

From the 2024 Cochrane systematic review, there was moderate-certainty evidence that emicizumab prophylaxis probably increased total adverse events compared with on-demand therapy in people with inhibitors (RR 1.97, 95% CI 1.26 to 3.10; one randomized controlled trial (HAVEN 1), 52 participants). No significant difference was seen between treatment groups for serious adverse events (RR 1.32, 95% CI 0.48 to 3.63). There was moderate-certainty evidence that other adverse events occurred more frequently with emicizumab prophylaxis compared with on-demand therapy (RR 1.94, 95% CI 1.22 to 3.09), with the most frequently reported adverse events being injection-site reactions (24%), upper respiratory tract infections (21%), fatigue (9%), headache (9%) and arthralgia (6%). For people

without inhibitors, there was moderate-certainty evidence that emicizumab prophylaxis (either dose) was associated with more adverse events (1.5 mg/kg weekly: RR 2.83, 95% CI 1.47 to 5.47; 3 mg/kg bi-weekly: RR 1.71, 95% CI 1.06 to 2.77). No differences were seen between emicizumab (either dose) or on-demand therapy for serious adverse events. Other adverse events occurred more frequently with emicizumab (1.5 mg/kg weekly: RR 3.50, 95% CI 1.66 to 7.39; 3.0 mg/kg bi-weekly: RR 3.39, 95% CI 1.60 to 7.18). The most commonly reported adverse events with emicizumab 1.5 mg/kg weekly and 3 mg/kg twice a week were injection-site reactions (25% and 20%), upper respiratory tract infections (both 11%), nasopharyngitis (6% and 17%), arthralgia (19% and 17%), headache (8% and 11%) and influenza (3% and 9%) (*3*).

In the HAVEN 1 trial, 198 adverse events were reported in 103 participants receiving emicizumab. All but one were of mild intensity and resolved. Events occurring in at least 5% of participants were injection-site reactions (15%), headache (12%), upper respiratory tract infection (9%), fatigue and arthralgia (both 6%). Twelve serious adverse events occurred in nine participants including thrombotic microangiopathy and thromboembolism in two participants each who had received multiple infusions of activated prothrombin complex concentrate while receiving emicizumab prophylaxis before event onset (*6*). These thrombotic events led to the United States Food and Drug Administration including a boxed warning in the emicizumab product label about concomitant use of emicizumab and activated prothrombin complex concentrate.

In the HAVEN 2 trial, 712 adverse events were reported in 82 participants receiving emicizumab. All were non-serious and resolved without treatment. Twenty-one serious adverse events were reported, with only a single report of development of anti-drug antibodies being assessed by trial investigators as being treatment related. The most common adverse events were nasopharyngitis (27.5%) and injection-site reactions (30.7%). No thromboembolic events were reported (*8*).

In the HAVEN 4 trial, 148 adverse events were reported in 30 participants receiving emicizumab, of which only one was serious (rhabdomyolysis) and considered unrelated to treatment. The most common adverse events deemed to be treatment-related were injection-site reactions (22%), chills, pre-syncope, erythema, and rash (2% each). No thrombotic events were reported. Two participants developed anti-drug antibodies (*10*).

The STASEY trial assessed the safety of emicizumab prophylaxis as the primary endpoint. The median duration of exposure to emicizumab for the evaluable population ($n = 193$) was 103.1 weeks. A total of 800 adverse events were reported in 163 participants. The most frequently reported adverse events occurring in ≥ 5% of participants receiving emicizumab were arthralgia (17.1%), nasopharyngitis (15.5%), and headache (15.0%). Injection-site reactions were

reported in 11.4% of participants, with most assessed as being treatment related. Fifty serious adverse events were reported in 31 participants, but only one was considered to be treatment related (a catheter-site abscess) which resolved with treatment. No study participants experienced a thrombotic microangiopathy. Thrombotic events reported in two participants were considered unrelated to treatment (*11*).

In the HAVEN 3 trial, 543 adverse events were reported in 127 participants. The most common adverse events reported in ≥ 5% of participants were injection-site reactions (25%), arthralgia (19%) and nasopharyngitis (12%). Fourteen serious adverse events were reported, but none were considered to be related to treatment. No deaths, thrombotic microangiopathy or thromboembolic events were reported (*13*).

In the HAVEN 5 trial, 185 adverse events were reported in 44 participants, the majority of which were grade 1 or 2. The most commonly reported adverse events were upper respiratory tract infection (27.1%) and injection-site reactions (12.9%). No deaths, thrombotic microangiopathy, or thromboembolic events were reported. Treatment-induced anti-drug antibodies were detected in 12.5% of evaluable participants, including one with neutralizing potential (*16*).

In the HAVEN 7 trial in infants, at the time of primary analysis, no intracranial haemorrhage events had occurred, no adverse events led to study discontinuation or treatment changes, and no new safety signals were identified. A total of 631 adverse events were reported in 55 participants. All treatment-related adverse events were grade 1 injection-site reactions. No thrombotic microangiopathy or thromboembolic events were reported (*17*).

A 2021 study evaluated the development of anti-emicizumab antibodies in people with haemophilia A receiving emicizumab, pooling data from the HAVEN 1-5, HOHOEMI and STASEY studies) (*23*). The study evaluated immunogenicity data for 668 participants (98 children aged < 12 years and 570 adolescents and adults aged ≥ 12 years). All participants were male and had a median age of 28 years. Most participants (62.1%) had FVIII inhibitors at baseline. Median emicizumab exposure was of 103.1 weeks (IQR 82.4 to 148.1). Results showed that 34 participants (5.1%) developed anti-drug antibodies after exposure to emicizumab. Incidence was similar in children and adolescents/adults. In 14/34 (41.2%) participants, anti-drug antibodies were transient, detected only at a single time point. Among the remaining 20 participants with anti-drug antibodies, 15 (75.0%) had no detectable antibodies at the last time point assessed, after a median duration of positivity for anti-drug antibodies of 20 weeks. In vitro analysis showed that anti-drug antibodies were neutralizing in 18/34 cases (52.9%) and associated with decreased emicizumab concentration in 4/34 (11.8%) participants, one of whom discontinued emicizumab due to loss of efficacy.

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of haemophilia are not available.

World Federation of Hemophilia guidelines for management of haemophilia (*24*) include the following recommendations in relation to emicizumab.

People with haemophilia A with inhibitors

- For patients with haemophilia A and inhibitors receiving emicizumab, conduct bovine chromogenic assays to monitor inhibitor levels.
- For patients with haemophilia A and inhibitors receiving emicizumab, undertake close clinical monitoring for thrombosis, adverse reactions and thrombotic microangiopathy.
- As emicizumab is used to prevent, but not treat, acute bleeds in patients with haemophilia A and inhibitors, clotting factor replacement therapy is recommended for acute bleeds.
- For patients with haemophilia A and inhibitors receiving emicizumab who have an acute bleed, clotting factor replacement therapy including FVIII is recommended for patients with low-responding inhibitors; recombinant FVIIa is preferred over activated prothrombin complex concentrates for patients with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.
- For patients with severe haemophilia A and inhibitors, emicizumab is preferred over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis.

People with severe haemophilia without inhibitors

- For patients with haemophilia A or B with a severe phenotype, it is strongly recommended that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.
- For patients with severe phenotype haemophilia A without inhibitors, prophylaxis with emicizumab will prevent haemarthrosis, and other spontaneous and breakthrough bleeding.

Costs/cost–effectiveness

Studies in people with haemophilia A with inhibitors

The application presented the findings from budget impact, cost–utility and cost–effectiveness studies identified through a literature search. Various studies from Brazil (25), Canada (26), France (27), India (28), Iran (Islamic Republic of) (29), Italy (30), Malaysia (31), Peru (32), Republic of Korea (33), Spain (34), South Africa (35) and United States of America (36) report emicizumab prophylaxis to be dominant and/or associated with cost-savings compared with bypassing agents as prophylaxis or as on-demand use in people with haemophilia A and inhibitors. Summaries of the findings were presented in the application.

Studies in people with haemophilia A without inhibitors

Evidence from economic studies of cost savings and cost–effectiveness of emicizumab show more variability for the treatment of people with severe haemophilia A without inhibitors. Studies show cost savings and cost–effectiveness with emicizumab compared to FVIII in India and the United States, but not in Europe and the United Kingdom of Great Britain and Northern Ireland.

A study in India evaluated the cost–effectiveness of emicizumab prophylaxis compared to on-demand therapy, and low-, intermediate-, and high-dose prophylaxis with FVIII in people with haemophilia A without inhibitors (37). In the base-case analysis, emicizumab was cost-effective compared with high-dose prophylaxis, with an incremental cost–effectiveness ratio of 27 869 Indian rupees (INR) per quality adjusted life year (QALY). Compared with on-demand therapy, intermediate-dose prophylaxis and low-dose prophylaxis, emicizumab prophylaxis was not shown to be cost-effective at a willingness-to-pay threshold of 1 x per capita gross domestic product with incremental cost–effectiveness ratios of INR 255 876, INR 264 592 and INR 305 398 per QALY, respectively. Emicizumab could be considered cost-effective compared with on-demand therapy, and low- and intermediate-dose prophylaxis if the willingness-to-pay threshold is greater than 1 x per capita gross domestic product. One-way sensitivity analysis highlighted emicizumab cost as the parameter with the greatest impact on incremental cost–effectiveness ratios.

An economic model study (funded by Genentech) estimated short- and long-term clinical and economic outcomes of emicizumab prophylaxis versus short-acting recombinant FVIII prophylaxis in people with haemophilia A without inhibitors from United States payer and societal perspectives (38). Over a lifetime horizon, the cumulative number of all treated bleeds and joint bleeds avoided on emicizumab versus recombinant FVIII prophylaxis were 278.2 and 151.7, respectively. Arthropathy and development of FVIII inhibitors were delayed. Total direct and indirect costs were lower for emicizumab versus recombinant

FVIII prophylaxis for all modelled time horizons (97 159 United States dollars (US$) versus US$ 331 610 at 1 year, US$ 603,146 versus US$ 1 459 496 at 5 years and US$ 15 238 072 versus US$ 22 820 281 over a lifetime horizon). Sensitivity analyses showed that clinical outcomes were sensitive to efficacy inputs, while economic outcomes were driven by the discount rate, dosing schedules and treatments after inhibitor development. The results for moderate to severe patients were consistent with findings in the severe population. Compared with short-acting recombinant FVIII, the model found that emicizumab prophylaxis led to superior patient outcomes and cost savings.

Another economic study from the United States evaluated the cost–effectiveness of emicizumab versus standard, extended and ultra-extended half-life recombinant FVIII products for prophylaxis in people with severe haemophilia A without inhibitors (*39*). Over a lifetime time horizon, emicizumab was estimated to be less costly (US$ 17.0 million versus US$ 24.0 million US$ 19.3 million and US$ 18.2 million for ultra-extended, standard and extended half-life recombinant FVIII) and more effective (18.61 QALYs versus 18.58 QALYs, 16.91 QALYs and 17.33 QALYs for ultra-extended, standard and extended half-life recombinant FVIII, respectively). Ultra-extended half-life recombinant FVIII was associated with fewer bleeds than emicizumab over a lifetime (26.58 versus 59.91), while emicizumab was associated with fewer bleeds over a lifetime compared with extended and standard half-life recombinant FVIII (59.91 versus 198.45 and 108.58, respectively). Results were robust to one-way and probabilistic sensitivity analyses. Overall, findings suggested that emicizumab was dominant over a lifetime compared with available recombinant FVIII prophylaxis in the United States of America.

Economic studies from Europe and the United Kingdom evaluated the cost–effectiveness of emicizumab compared with extended half-life recombinant FVIII as prophylaxis in people with haemophilia A without inhibitors. A cost-minimization study from the European health-care payer perspective found incremental savings over 5 years for extended half-life recombinant FVIII compared with emicizumab of 89.3 million euros (€) to €150.0 million in adolescents/adults and from €173.4 million to €253.2 million in children < 12 years. The model included costs for drug acquisition, emicizumab wastage and additional FVIII for breakthrough bleeds. Emicizumab wastage accounted for 6% and 26% of its total cost in adolescents/adults and children, respectively (using manufacturer's recommendations) (*40*). A cost–effectiveness study from the United Kingdom also compared extended half-life recombinant FVIII and emicizumab as prophylaxis in people with haemophilia A without inhibitors (*41*). The base-case analysis found that individualized prophylaxis with extended half-life recombinant FVIII was the dominant treatment strategy, with lower costs, more QALYs and fewer bleeds.

Availability

Emicizumab has regulatory approval for the treatment of children and adults with haemophilia A with inhibitors in 122 countries and without inhibitors in 112 countries.

Emicizumab is marketed in over 100 countries with 29 low- to middle-income countries accessing emicizumab through the World Federation of Hemophilia Humanitarian Aid Program (*42*).

Currently, no biosimilars of emicizumab are available.

Other considerations

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Committee recommendations

The Expert Committee acknowledged that the established standard of care for people with haemophilia A involves routine prophylaxis with plasma-derived or recombinant coagulation factor VIII (FVIII), or non-factor replacement therapy with emicizumab. Periodic, on-demand treatment with coagulation factors is used in situations of acute bleeds, in people with non-severe disease and for people with severe disease in low-income settings when prophylactic options are unavailable or unaffordable. The Committee noted that among people with haemophilia A receiving prophylaxis with FVIII replacement, about 30% develop inhibitors against FVIII, rendering further FVIII replacement ineffective. Inhibitor development is associated with increased morbidity and mortality.

The Committee considered that the systematic review, clinical trial and real-world evidence presented in the application supported the efficacy and safety of emicizumab as prophylactic treatment for adults and children with haemophilia A, both with and without FVIII inhibitors. Compared with no prophylaxis, and prophylaxis with FVIII or bypassing agents, emicizumab was demonstrated to provide meaningful reductions in bleeding rates and the use of bypassing agents, increases in the chance of being bleed-free, maintenance of joint function, reductions in surgical risks and caregiver burden, and improvements in health-related quality of life measurement scores. Most adverse effects were generally mild to moderate, and manageable. Serious thrombotic adverse events have been reported in some trials, associated with concomitant use of emicizumab and activated prothrombin complex concentrate. Overall, the Committee considered that the balance of benefits to harms of emicizumab for people with haemophilia A, with and without FVIII inhibitors was favourable.

The Committee noted that multiple economic and budget impact analyses have reported emicizumab prophylaxis to be dominant and/or cost-saving compared with bypassing agents as prophylaxis or as on-demand use in

people with haemophilia A and inhibitors. In people with haemophilia A without inhibitors, economic analyses produced varying cost–effectiveness findings. Nevertheless, the Committee noted that emicizumab has a high price, with prices varying across countries. The Committee noted that strategies to reduce the cost of emicizumab treatment, such as vial sharing and dose/dose interval modifications, are being successfully used in some settings to reduce the budget impact while safeguarding treatment benefits.

The Committee noted that emicizumab has wide global regulatory approval for treatment of adults and children with haemophilia A with inhibitors, and for adults and children with severe haemophilia A without inhibitors. Biosimilars are not currently available.

The Committee noted and appreciated the contributions submitted during the public consultation process for the application, indicating broad support for the proposal to include emicizumab on the Model Lists.

Based on these considerations, the Expert Committee recommended the inclusion of emicizumab to the core list of the EML and EMLc for prophylactic treatment in people with haemophilia A with and without FVIII inhibitors.

Further to this recommendation, and in recognition of the current high price of emicizumab, the Committee highlighted that the value of emicizumab prophylaxis is greatest in people with haemophilia A with FVIII inhibitors, in whom factor replacement is ineffective. In people with severe haemophilia A without FVIII inhibitors, prophylaxis with plasma-derived or recombinant FVIII may represent a better value and more affordable treatment option. In considering inclusion of emicizumab on national EMLs in resource-constrained settings, and in line with national needs, decision-makers may wish to prioritize/limit selection and use of emicizumab in the first instance to the population of people with haemophilia A with FVIII inhibitors. They may extend selection and use for people with severe haemophilia A without inhibitors when the price of emicizumab is lower and/or if resources allow.

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Phytomenadione – new formulation – EML and EMLc

Phytomenadione **ATC code: B02BA01**

Proposal

Addition of a new formulation of phytomenadione (injection, mixed micelle solution) to the EML and EMLc for prophylaxis and treatment of haemorrhagic disease of newborns and of haemorrhage due to severe hypoprothrombinaemia.

Applicant

Cheplapharm Arzneimittel GmbH, Greifswald, Germany

WHO technical department

The Department of Maternal, Newborn, Child and Adolescent Health and Ageing reviewed the application and advised that it supported the inclusion of phytomenadione mixed micelle (MM) solution on the EMLc for prevention and treatment of haemorrhagic disease of the newborn.

EML/EMLc

EML and EMLc

Section

10.2 Medicines affecting coagulation

Dose form(s) & strengths(s)

Injection: 2 mg/0.2 mL, 10 mg/mL (MM solution) in ampoule

Core/complementary

Core

Individual/square box listing

Individual

Background

The proposed formulation of phytomenadione had not been previously evaluated for inclusion on the Model Lists. The Model Lists currently include standard injection and oral dosage forms of phytomenadione.

Public health relevance

The public health relevance of phytomenadione in the prevention and treatment of vitamin K deficiency bleeding in newborns, and for prevention and treatment of haemorrhage due to severe hypoprothrombinaemia due to various causes is well established. Phytomenadione has been included on the Model Lists for these indications since the first list was published in 1977.

Summary of evidence: benefits

The application presented summaries of four published reports in which phytomenadione mixed micelle solution was compared with existing phytomenadione formulations in paediatric patients.

A 1998 randomized controlled trial compared orally administered phytomenadione MM with a standard intramuscular preparation during the first 8 weeks of life in 156 exclusively breastfed infants (*1*). Participants were randomized to receive 2 mg oral phytomenadione ($n = 79$) or 1 mg intramuscular phytomenadione ($n = 77$) at birth, with additional oral doses at 7 and 30 days. Prothrombin time, plasma vitamin K1 and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were monitored at 14, 30 and 56 days. Prothrombin times did not differ between the two groups. Plasma vitamin K1 levels were higher in the oral group at 14 days and 56 days. PIVKA-II levels were raised in 47% of infants at birth but normalized by 14 days in both groups, with no raised values at 30 days and only three raised values in the intramuscular group at 56 days.

A 1997 randomized study examined the pharmacokinetics of two orally administered phytomenadione preparations in 30 exclusively breastfed newborns (*2*). Concentrations of vitamin K, PIVKA-II and total bound bilirubin were measured at 24 hours, 4 days and 24 days after birth. Median plasma vitamin K1 levels were higher in the MM group at all time points but was only significantly different at 4 days. PIVKA-II was detectable in fewer infants in the MM group at 24 hours (21% versus 75%) and 4 days (14% versus 50%). No infants had detectable PIVKA-II at 24 days.

A 1992 study evaluated the pharmacokinetics and safety phytomenadione MM and standard phytomenadione administered parenterally in 71 infants with chronic cholestasis (*3*). The study found no significant differences between treatment groups in blood parameters, including total and conjugated bilirubin, transaminases, gamma-glutamyl transferase and alkaline phosphatase. Both formulations were well tolerated. Among nine infants with biliary atresia randomized to receive a single oral dose of 20 mg phytomenadione ($n = 3$) or 20 mg phytomenadione MM ($n = 3$) or 10 mg of phytomenadione MM administered intramuscularly. ($n = 3$), low serum vitamin K1 levels of were observed after oral phytomenadione. However, the same dose of oral phytomenadione MM or

10 mg intramuscular phytomenadione MM both resulted in very high serum vitamin K1 levels. No adverse events were reported. Long-term administration was also investigated in this study: 22 infants and children received 10 mg phytomenadione intramuscularly twice a week for 6 months, followed by 10 mg oral or intramuscular phytomenadione MM for an additional 3 months. The highest vitamin K levels were observed in the intramuscular group.

A 2003 surveillance study in Germany assessed the efficacy of oral phytomenadione MM versus other oral phytomenadione preparations in preventing late vitamin K deficiency bleeding (*4*). Between 1997 and 2000, about 1.8 million and 1.3 million newborns were exposed to phytomenadione MM and other phytomenadione formulations, respectively. In total, 29 infants had confirmed vitamin K deficiency bleeding, of whom 17 had been given recommended doses of phytomenadione: seven received the MM formulation, nine received other formulations and one received both. The rate of late vitamin K deficiency bleeding was 0.44 per 100 000 (95% confidence intervale (CI) 0.19 to 0.87 per 100 000) in children given the MM formulation compared with 0.76 per 100 000 (95% CI 0.36 to 1.39 per 100 000) in children given other preparations. No significant differences were seen between the formulations. However, the MM formulation was effective in maintaining adequate vitamin K levels and preventing vitamin K deficiency bleeding.

The application also presented summaries of nine unpublished clinical studies conducted by F. Hoffman-LA Roche that included 182 infants treated with oral, intramuscular or intravenous phytomenadione MM compared with existing phytomenadione formulations.

The application presented a summary of one published report in which phytomenadione MM solution was compared with existing phytomenadione formulations in adults.

The pharmacokinetics and tolerance of intravenous and intramuscular phytomenadione MM were evaluated in 30 healthy adult volunteers in a 1996 study using an open randomized crossover design (*5*). Participants received phytomenadione 10 mg via intravenous or intramuscular injection, and blood samples were collected up to 12 hours after intravenous injection and up to 72 hours after intramuscular injection. Phytomenadione MM was well tolerated after both routes of administration. Systemic availability following intramuscular administration was less than 65% in 20% of participants, indicating irregular and unpredictable absorption from the depot site.

Summary of evidence: harms

Adverse events associated with phytomenadione formulations were evaluated in a worldwide post-marketing surveillance programme (*6*). Data were collected from spontaneous reports, clinical trials, and post-marketing surveillance.

Between 1974 and 1995, an estimated 635 million adults and 728 million children were prescribed phytomenadione formulations. A total of 404 adverse events were reported in 286 individuals, 387 of which were associated with standard phytomenadione formulations. Most of the serious adverse events (117/120) were associated with standard formulations, including 85 probable anaphylactoid reactions (six fatal). Most of the adverse events with phytomenadione MM were minor injection-site reactions (13/17).

The application also presented summaries of various unpublished clinical studies conducted by F. Hoffman-LA Roche in adults and children that suggested an acceptable safety profile for phytomenadione MM.

Additional evidence

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WHO guidelines

The WHO recommendations on newborn health include a strong recommendation (moderate-quality evidence) for all newborns to be given 1 mg of vitamin K intramuscularly after birth (after the first hour during which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated). The guidelines also include a strong recommendation (moderate-quality evidence) for neonates at especially high risk of bleeding, e.g. requiring surgical procedures, those with birth trauma, preterm newborns and those exposed in utero to maternal medication known to interfere with vitamin K, to be given 1 mg vitamin K intramuscularly (7).

Costs/cost–effectiveness

The application reported that the price per ampoule of phytomenadione MM ranges from 0.26 United States dollars (US$) to US$ 3.00 (mean US$ 1.63) for the 2 mg/0.2 mL strength, and from US$ 0.35 to US$ 4.00 (mean US$ 2.18) for the 10 mg/mL strength. Average treatment costs were reported in the application as US$ 3.26 per dose in paediatric patients and US$ 2.18 per dose in adults.

Availability

Phytomenadione MM formulation has wide global regulatory approval. It is actively marketed in more than 40 countries, with ongoing registration processes reported in additional countries. The application reported that it is provided to non-profit organizations such as United Nations Children's Fund and Médecins Sans Frontières.

Other considerations

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Committee recommendations

The Expert Committee noted that phytomenadione is currently included in the Model Lists as oral and injectable formulations as an essential medicine for prophylaxis and treatment of haemorrhagic disease of newborns and for treatment and prophylaxis of haemorrhage due to severe hypoprothrombinaemia. The proposed new formulation is a mixed micelle solution formulation that can be administered intravenously, intramuscularly or orally. It has enhanced solubility and bioavailability, and a faster and more reliable onset of action.

The Committee considered that the proposed formulation represents an additional effective treatment option that offers flexibility for administration, with evidence of comparable efficacy and safety to currently listed formulations. In the case of haemorrhagic disease of newborns, it allows single-dose intramuscular injection at birth, which is crucial in settings where follow-up for multi-dose oral regimens is unreliable.

The Expert Committee therefore recommended the inclusion of the proposed mixed micelle formulation of phytomenadione on the EML and EMLc for the same indications for which the existing formulations are currently listed.

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Section 11: Blood products, coagulation factors and plasma substitutes

11.1 Blood and blood components

Cryoprecipitate, pathogen-reduced and non-pathogen-reduced, plasma-derived clotting factor concentrates – changes to listing – EML and EMLc

Cryoprecipitate, pathogen-reduced and non-pathogen-reduced	**ATC code: B05AA02**
Plasma-derived coagulation factor VIII	**ATC code: B02BD02**
Plasma-derived coagulation factor IX	**ATC code: B02BD04**
Plasma-derived coagulation factor IX complex	**ATC code: B02BD01**

Proposal

The application proposed:

i. To remove cryoprecipitate, non-pathogen-reduced for all listed indications;
ii. To limit the listed indications of cryoprecipitate, pathogen-reduced to those outside of haemophilia A and von Willebrand disease;
iii. To transfer the current listings of plasma-derived coagulation factors VIII and IX from the complementary to the core list; and
iv. To remove plasma-derived coagulation factor IX complex as a therapeutic alternative to plasma-derived coagulation factor IX for the treatment of haemophilia B.

All proposals apply to listings on both the EML and EMLc.

Applicant

World Federation of Hemophilia

WHO technical department

The blood and other products of human origin team within the Department of Health Products, Policy and Standards reviewed and provided comments on the application.

The technical team proposed that cryoprecipitate, non-pathogen-reduced be retained on the Model Lists, in alignment with results of a 2024 WHO international survey on the availability and clinical use of cryoprecipitates, as well as input from the International Society of Blood Transfusion, the WHO Advisory Group for Blood Regulation, Availability and Safety (AG-BRAS) and the Shanghai

Blood Centre (which serves as a WHO collaborating centre for blood transfusion services). The team highlighted that ongoing listing would be consistent with the current listing of other non-pathogen-reduced blood components, including whole blood, plasma, platelets and red blood cells. The technical team emphasized that strict blood screening for transfusion-transmitted infections should be applied during the production of cryoprecipitate and other blood components to reduce the risk of transfusion-transmitted infections.

The technical team proposed that the listing for cryoprecipitate, pathogen-reduced, should not be limited only to non-haemophilia indications. This proposal is based on the results of the 2024 WHO international survey, which indicated that the product continues to play a crucial role in ensuring treatment accessibility for acute bleeding conditions where recombinant or plasma-derived coagulation factors are not available.

In alignment with discussion and input from the International Society of Blood Transfusion, the WHO AG-BRAS and the Shanghai Blood Centre, the technical team supported the transfer of plasma-derived coagulation factors VIII and IX from the complementary to the core list.

In alignment with discussion and input from the International Society of Blood Transfusion, the WHO AG-BRAS and the Shanghai Blood Centre, the technical team supported the removal of coagulation factor IX complex as a therapeutic alternative to plasma-derived coagulation factor IX due to an increased risk of thrombosis.

EML/EMLc

EML and EMLc

Section

11.1 Blood and blood components

Dose form(s) & strengths(s)

As currently listed.

Core/complementary

Core

Individual/square box listing

Square box for cryoprecipitate, pathogen-reduced, with cryoprecipitate, native as a specified therapeutic alternative.

Individual listings for all other medicines.

Background

In 2023, the Expert Committee considered an application from the International Society of Blood Transfusion for the addition of pathogen-reduced cryoprecipitate (cryoprecipitate-PR) to the EML and EMLc for replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII, and as a therapeutic alternative to coagulation factor VIII for treatment of haemophilia A in settings where coagulation factor VIII is not available or affordable. Listing was proposed as a square box listing for cryoprecipitate-PR, with non-pathogen reduced cryoprecipitate specified as a therapeutic alternative.

The Committee recognized that insufficient access to clotting factor replacement products contributes to early death in patients with bleeding disorders. Accessibility to these products is especially problematic in low- and middle-income countries where many patients have no access to treatment.

The Committee considered that the evidence and extensive clinical experience suggest that cryoprecipitate is superior to plasma for replacement of certain clotting factors in a variety of indications in adults and children. However, the Expert Committee noted that concentrated clotting factors remain the preferred treatment for many bleeding disorders and should be prioritized for selection and use wherever possible. The Committee noted and agreed with the WHO Blood Regulators Network position statement and emphasized that cryoprecipitate-PR ought only to be used in settings where commercial clotting factors are unaffordable or unavailable. The Committee was not in the position to recommend specific methods of pathogen reduction but considered that cryoprecipitate-PR developed using validated, approved pathogen-reduction methods should be ensured.

The Committee also noted that comparative evidence for cryoprecipitate-PR versus non-pathogen-reduced cryoprecipitate was limited but acknowledged that pathogen reduction can eliminate major risks of transmission of bloodborne infectious agents and increase the safety of administration. While there is a risk of alloimmunization and allergic transfusion reaction, these adverse events are lower than rates reported for other blood components, including fresh frozen plasma.

The Expert Committee therefore recommended the inclusion of cryoprecipitate-PR on the core list of the EML and EMLc for use in the replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate for patients with haemophilia A in settings where coagulation factor VIII is unavailable of unaffordable. The Committee also recommended that non-pathogen-reduced cryoprecipitate be included in the Model Lists as a therapeutic alternative given that transition to cryoprecipitate-PR at the country level may take some time. The Committee acknowledged

that solvent and detergent virus inactivation technologies and medical devices used in the plasma fractionation industry are gaining momentum and are being adopted by an increasing number of blood establishments and national blood service centres. For this reason, the Committee considered that removal of non-pathogen-reduced cryoprecipitate from the Model Lists as a therapeutic alternative to cryoprecipitate-PR should be considered at the earliest opportunity unless an application is received to support its retention.

The Committee emphasized the requirement that all blood, blood components and plasma derivates used as essential medicines should comply with WHO requirements developed by the WHO Expert Committee on Biological Standardization. The Committee also emphasized that blood donor and donation screening for infections before use of blood products should always be implemented.

Public health relevance

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Summary of proposals

The rationale for the proposals made by the World Federation of Hemophilia is based on the following issues.

- Non-pathogen-reduced cryoprecipitate has inadequate efficacy and poses a number of safety risks compared with available alternatives.
- Many lower-income countries in which cryoprecipitate is still used for the treatment of haemophilia A and von Willebrand disease, especially in situations of urgent bleeding, also face significant challenges in blood safety, with higher prevalence rates of transfusion-transmitted infection markers than in high-income countries.
- A significant residual risk of infection exists in countries where there is a high background prevalence of transfusion-transmitted infection and where donor blood screening regimens use relatively insensitive tests. Additionally, the risk of infection is increased for people with haemophilia A and von Willebrand disease as a result of the need to pool individual cryoprecipitate units to achieve a therapeutic dose.
- Cryoprecipitate cannot be administered prophylactically to prevent bleeding episodes in people with haemophilia A and von Willebrand disease and therefore is only used to treat existing bleeding events.
- Cryoprecipitate contains variable amounts of factor VIII and fibrinogen, resulting in less reliable dosing for treatment of bleeds compared with coagulation factor concentrates.

- Currently available technologies for producing pathogen-reduced cryoprecipitate have a limited capacity to inactivate viruses without a lipid envelope (e.g. hepatitis A, parvovirus B19).
- There is inconsistency with listing of cryoprecipitate on the core list and listing of plasma-derived coagulation factor concentrates on the complementary list. Coagulation factor concentrates are self-administered by patients and are the standard of care for prophylaxis in haemophilia and von Willebrand disease.
- Coagulation factor IX complex has been associated with an increased risk of thrombosis when used in the treatment of haemophilia B.

Summary of evidence: harms

Not applicable

Additional evidence

Not applicable

WHO guidelines

Not applicable

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

In response to the 2023 Expert Committee's recommendation that non-pathogen-reduced cryoprecipitate be removed from the Model Lists in 2025, a proposal was received from the International Society of Blood Transfusion in support of its retention. The following reasons were cited for retaining non-pathogen-reduced cryoprecipitate on the Model lists included:

- Indications for the use of cryoprecipitate extend beyond haemophilia A, especially to treat deficiencies of fibrinogen associated with massive haemorrhage in the settings of trauma and peripartum bleeding and to treat major bleeding episodes in von Willebrand disease.

- Access to pathogen-reduced cryoprecipitate is limited globally because the technologies available to produce it are not in wide use. Authorized devices for virus-inactivation are costly and/or relatively new to the market.
- Removal of non-pathogen-reduced cryoprecipitate would be inconsistent with continued listing of fresh frozen plasma and platelets which are widely used as non-virus-inactivated blood components despite the existence of applicable pathogen reduction technologies in higher income countries.
- Continued listing of non-pathogen-reduced cryoprecipitate serves to remind governments of the duty to ensure that this and other blood and blood components should be made available with full attention to assuring their microbial safety. This requirement must be met through implementation of good manufacturing practices that include selection of low-risk donors, donation testing for evidence of transfusion transmissible infectious diseases, aseptic collection and sterile preparation processes, properly controlled storage conditions, and appropriate clinical use.

The International Society of Blood Transfusion further highlighted the need to stress the importance of the preferred use of pathogen-reduced over non-pathogen-reduced cryoprecipitate as an alternative to coagulation factor VIII in haemophilia A due to the added risks from repeated administration. Similarly, pathogen-reduced cryoprecipitate is strongly preferred over non-pathogen-reduced cryoprecipitate for treatment of bleeding episodes in von Willebrand disease. Infectious risks from multiple exposures to non-pathogen-reduced products made from pooled plasma units are significant, particularly in the same settings where access to industrially manufactured coagulation factors is limited or unavailable due to resource limitations.

Committee recommendations

The Expert Committee considered the request made by the World Federation of Hemophilia for changes to the listings of non-pathogen-reduced cryoprecipitate, pathogen-reduced cryoprecipitate and plasma-derived coagulation factors on the EML and EMLc. In making its recommendations, the Committee also took into consideration the following:

- the recommendation of the 2023 Expert Committee to remove non-pathogen-reduced cryoprecipitate from the Model Lists at the 2025 meeting unless an application was received in support of its retention;

- the strong objection from the World Federation of Hemophilia to the listing of non-pathogen-reduced cryoprecipitate for all listed indications, and to the listing of pathogen-reduced cryoprecipitate as an alternative to coagulation factor concentrates in the treatment of haemophilia A and von Willebrand disease;
- the request received from the International Society of Blood Transfusion in support of the retention of non-pathogen-reduced cryoprecipitate; and
- contributions received from stakeholders during the public consultation period and the input from the Blood and Other Products of Human Origin team at WHO.

After consideration of all relevant factors, the Expert Committee made the following recommendations.

The Expert Committee recommended that non-pathogen-reduced (i.e. native) cryoprecipitate and pathogen-reduced cryoprecipitate be removed from the Model Lists for use in prophylactic treatment of haemophilia A and von Willebrand disease. The Committee recognized the increased risks of transfusion-transmitted infections associated with repeated transfusions in patients with these conditions.

The Committee acknowledged that there remains a role for cryoprecipitate as on-demand management of acute bleeding episodes and in patients with haemophilia A and von Willebrand disease undergoing surgery in circumstances where preferred alternatives are not available. The Committee acknowledged that cryoprecipitate may be the only available treatment option in some settings and that despite the iatrogenic risks, clinical circumstances clearly justify its use. In such cases, pathogen-reduced cryoprecipitate is preferred over non-pathogen-reduced cryoprecipitate.

The Expert Committee recommended that non-pathogen-reduced cryoprecipitate be retained on the EML and EMLc as a therapeutic alternative to pathogen-reduced cryoprecipitate for use in cases of life-threatening major haemorrhage and rapid loss of blood volume (e.g. severe trauma, major surgery, obstetric haemorrhage). The Committee considered that at this time and under the aforementioned clinical circumstances, native cryoprecipitate is still a therapeutic alternative to coagulation factors or pathogen-reduced cryoprecipitate when these are not available. In such situations, the iatrogenic risks are clearly outweighed by the potential life-saving benefits of native cryoprecipitate. The Committee recognized the importance of preferential use of coagulation factor concentrates or pathogen-reduced cryoprecipitate over native cryoprecipitate due to the reduced risk of transfusion-transmitted infections. However, the Committee noted that widespread global access to pathogen-reduced cryoprecipitate is currently limited. In settings where pathogen-reduced cryoprecipitate is not available, native cryoprecipitate is a last resort alternative.

The Expert Committee recommended that the current listings for plasma-derived coagulation factors VIII and IX be transferred from the complementary to the core list of the EML and EMLc. For consistency across listings for other medicines used in the treatment of haemophilia and von Willebrand disease, the Committee recommended that the listing for desmopressin also be transferred from the complementary to the core list.

The Expert Committee recommended the removal of coagulation factor IX complex as a therapeutic alternative under the square box listing of plasma-derived coagulation factor IX on the EML and EMLc given the increased risk of thrombosis associated with this product.

11.3 Coagulation factors

Recombinant coagulation factors – addition – EML and EMLc

Coagulation factor VIII, recombinant	**ATC code: B02BD02**
Coagulation factor IX, recombinant	**ATC code: B02BD04**

Proposal

Addition of recombinant coagulation factor VIII (FVIII) for adults and children with haemophilia A and of recombinant coagulation factor IX (FIX) for adults and children with haemophilia B on the EML and EMLc.

Applicant

World Federation of Hemophilia

WHO technical department

The blood and other products of human origin team within the Department of Health Products, Policy and Standards reviewed the application and supported the inclusion of recombinant coagulation factors on the EML and EMLc.

EML/EMLc

EML and EMLc

Section

11.3 Coagulation factors

Dose form(s) & strengths(s)

Lyophilized powder for solution for injection: 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU in vial

Core/complementary

Core

Individual/square box listing

Individual

Background

Plasma-derived coagulation FVIII and FIX have been included on the EML and EMLc since 1979 and 2007, respectively. In 2007, in consideration of the inclusion of plasma-derived coagulation factors on the first EMLc, the EMLc Subcommittee recognized that plasma fractions were essential medicines for

both adults and children. The Subcommittee noted comments that recombinant products should be used in preference to dried and plasma-derived products and considered that recombinant products would be covered by the existing square box listings (*1*).

At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for plasma-derived coagulation factors VIII and IX be reviewed and updated in 2023 (*2*). Thus, the Secretariat invited the World Federation of Hemophilia to submit an application reviewing the therapeutic alternatives for these medicines.

At its meeting in 2023, the Expert Committee considered a submission from the World Federation of Hemophilia addressing the request of the 2021 Expert Committee. The submission recommended the inclusion of recombinant factors VIII and IX as therapeutic alternatives to their respective plasma-derived counterparts based on: human-derived and recombinant coagulation factor products being classified with the same Anatomical Therapeutic Chemical (ATC) code; the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-derived products and would be captured under the existing square box listing; and recommendations in Federation's guidelines for the management of haemophilia. A comprehensive review of the available evidence was not provided in the application. In making its recommendation, the 2023 Committee noted that when plasma-derived coagulation factors were considered for inclusion on the first EMLc in 2007, the Committee at that time considered that recombinant products would be covered by the existing square box listings. However, a comprehensive review of the evidence for the comparative efficacy, safety and cost/cost–effectiveness of recombinant products had not been conducted nor evaluated at that time. The 2023 Committee therefore recommended that a full application, compliant with EML application requirements, be requested so that the available evidence could be evaluated (*3*).

Public health relevance

The public health relevance of treatments for haemophilia is well established.

According to the 2022 World Federation of Hemophilia annual global survey, more than 250 000 people (mostly males) were living with haemophilia. The incidence of haemophilia A was about 1 in 4000 to 5000 live male births, about 50–60% of whom have severe disease (FVIII activity < 1% of normal), which is associated with high rates of spontaneous bleeding that may necessitate prophylactic treatment. The incidence of haemophilia B was about 1 in 15 000 to 30 000 live male births, of whom about a third to a half have severe disease (FIX activity < 1% of normal) (*4*). For haemophilia A, the estimated prevalence per

100 000 males is 17.1 cases for all severities and 6.0 cases for severe haemophilia A. For haemophilia B, the estimated prevalence per 100 000 males is 3.8 cases for all severities of haemophilia B and 1.1 cases for severe haemophilia B (5). Globally, almost 12 000 females with haemophilia have been identified (4).

Studies have shown that lack of treatment results in lower life expectancy with life expectancy disadvantages of about 93% for people with haemophilia in low-income countries, 77% in lower middle-countries and 64% in upper middle-countries (5).

Until the introduction of coagulation factor concentrates in the mid-1960s, the average life expectancy for boys with severe haemophilia was less than 20 years and quality of life was generally afflicted by joint bleeding complications and, in many cases, intracranial haemorrhage (6). Those who survived had complications of frequent bleeding involving their weight-bearing joints, resulting severe and incapacitating joint damage. The incidence of intracranial haemorrhage was about 1 in 200 per year and often resulted in severe permanent brain damage in those who survived the initial bleeding episode (6, 7).

Summary of evidence: benefits

Clotting factor concentrates are used in the treatment of haemophilia as on-demand/episodic factor replacement administered after the onset of bleeding and as prophylactic therapy administered regularly to provide sufficient FVIII and FIX to prevent spontaneous bleeding and to have normal coagulation function after any trauma (6). Substantial evidence exists that prophylaxis is associated with improved joint outcomes, decreased physical pain and better health-related quality of life compared with episodic treatment (8). Without prophylactic treatment, individuals with haemophilia may have on average two to five spontaneous bleeding episodes each month including joint bleeds and deep-muscle haematomas. They may also experience prolonged bleeding or excessive pain and swelling from minor injuries, surgery and tooth extractions (9). Accordingly, primary prophylaxis with clotting factor concentrates has become the standard of care for people with severe haemophilia.

A 2022 systematic review and meta-analysis of nine randomized controlled trials compared the effects of factor replacement therapies on people with haemophilia (10). Six of the trials compared episodic versus prophylactic treatment in patients with haemophilia A, with two studies using plasma-derived FVIII and four using recombinant FVIII. Meta-analyses of these studies found very-low-certainty evidence of significant differences in annualized bleeding rates and annualized joint bleeding rates favouring prophylaxis. Compared with episodic treatment, the annualized bleeding rate was lower for: low-dose prophylaxis (ratio of means (RM) 0.27, 95% confidence interval (CI) 0.17 to 0.43; two randomized controlled trials, 71 participants); intermediate-dose

prophylaxis (RM 0.15, 95% CI 0.07 to 0.36; four randomized controlled trials, 237 participants); and high-dose prophylaxis (RM 0.07, 95% CI 0.04 to 0.13; one randomized controlled trial, 52 participants). Similarly, compared with episodic treatment, annualized joint bleeding rates were lower for: low-dose prophylaxis (RM 0.17, 95% CI 0.06 to 0.43; two randomized controlled trials, 71 participants); intermediate-dose prophylaxis (RM 0.14, 95% CI 0.07 to 0.27; four randomized controlled trials, 237 participants); and high- dose prophylaxis (RM 0.08, 95% CI 0.04 to 0.16; one randomized controlled trial, 52 participants). Meta-analysis also showed that patients who received intermediate-dose prophylaxis had a lower rate of radiographical findings compared with those who used episodic treatment (risk ratio (RR) 0.36, 95% CI 0.18 to 0.71; two randomized controlled trials, 95 participants). In comparison to the on-demand group, the low-dose group had a lower median score on the Haemophilia Joint Health Score.

One of the studies evaluated administration of recombinant FIX at the same dose at different time intervals (50 IU/kg twice weekly versus 100 IU/kg weekly) compared with on-demand therapy (*11*). Both prophylaxis regimens were significantly reduced annualized bleeding rates compared with on-demand therapy: mean annualized bleeding rates 35.1 with on-demand therapy, 2.6 with twice weekly prophylaxis and 4.6 with weekly prophylaxis. No significant difference was seen in mean annualized bleeding rates between prophylaxis regimens. The mean annualized joint bleeding rate was 25.4 in the on-demand group, 1.9 in the twice-weekly group and 3.6 in the weekly group (no P-value provided). These results had a very low certainty of evidence.

Prophylactic use of FVIII and FIX has been shown to offer better outcomes for patients with moderate or severe haemophilia compared with on-demand use, including in resource-constrained settings (*12*–*15*).

Summary of evidence: harms

Viral safety and purity

In the late 1970s to early 1980s, thousands of people with haemophilia globally were infected with human immunodeficiency virus (HIV) and hepatitis C virus through contaminated plasma-derived factor concentrates and blood products. This led to the development of viral inactivation technologies and measures in manufacturing, most commonly using a combination of solvent detergent exposure, nanofiltration and pasteurization or dry heat exposure. These techniques prevent transmission of lipid-enveloped viruses such as HIV and hepatitis C virus but not non-lipid-enveloped pathogens such as parvovirus B19 (*16*).

The implementation of donor selection, plasma screening, nucleic acid testing, robust viral inactivation processes and post-marketing surveillance over the past 40 years has led to a substantial reduction in bloodborne infections in patients with haemophilia treated with plasma-derived and recombinant products (*17*).

Both types of coagulation factor are now manufactured in adherence to good manufacturing practices and have strong safety records related to transmission of viruses such as HIV and hepatitis C virus and other transmissible agents such as prions. However, plasma-derived factor concentrates always carry a theoretical risk of contamination with transmissible viruses and most recombinant factor concentrates have trace amounts of human proteins which present an extremely small risk of viral infectivity.

Immunogenicity and inhibitor formation

An important complication of treatment of haemophilia with coagulation factor concentrates is the formation of inhibitors (neutralizing alloantibodies) against FVIII or FIX, potentially leading to failure of replacement therapy and increasing the risk of bleeding episodes. About 30% of patients with severe haemophilia A and between 9% and 23% of patients with severe haemophilia B are reported to develop inhibitors. Inhibitor development is associated with increased morbidity and mortality (*18*).

The SIPPET study was a randomized controlled trial that evaluated the incidence of FVIII inhibitors in previously untreated or minimally treated boys with severe haemophilia A treated with plasma-derived FVIII containing von Willebrand factor or recombinant FVIII (*19*). A total of 264 participants were randomized in a 1:1 ratio to receive plasma-derived or recombinant FVIII, 251 of whom received treatment and were analysed. For the primary endpoint of all inhibitors, development of inhibitors was reported in 29/125 (23.2%) patients who received plasma-derived FVIII, and 47/126 (37.3%) patients who received recombinant FVIII. The cumulative inhibitor incidence for plasma-derived FVIII and recombinant FVIII was 26.7% and 44.5%, respectively. In Cox regression models for the primary endpoint, recombinant FVIII was associated with a significantly higher incidence than plasma-derived FVIII (hazard ratio (HR) 1.87, 95% CI 1.17 to 2.96). For high-titre inhibitors, the HR was 1.69 (95% CI 0.96 to 2.98). When second-generation full-length recombinant FVIII was excluded from the analysis, the results were similar for all inhibitors (HR 1.98, 95% CI 0.99 to 3.97) and also for high-titre inhibitors (HR 2.59, 95% CI 1.11 to 6.00).

An observational study conducted by the RODIN study group evaluated data from 574 previously untreated patients with severe haemophilia A receiving coagulation factors to determine the risk of inhibitor development (*20*). Inhibitor development was reported in 32.4% of participants. Plasma-derived and recombinant coagulation factors showed similar risk of inhibitor development (adjusted HR 0.96, 95% CI 0.62 to 1.49). However, there was a higher incidence of inhibitor formation associated with second-generation full-length recombinant products produced in baby hamster kidney cells compared with third-generation full-length recombinant products.

Another observational study investigated the difference in inhibitor development between different brands of recombinant FVIII in 407 previously untreated children with severe haemophilia A in the United Kingdom of Great Britain and Northern Ireland (*21*). Inhibitors developed in 118 (29%) participants. Of 128 participants who received Kogenate Bayer/Helixate NexGen, 45 (35%) developed an inhibitor compared with 42/172 (24%) who received Advate. The adjusted HR for all inhibitors for the former compared to the latter brand was 1.75 (95% CI 1.11 to 2.76; $P = 0.01$).

A French observational study compared the incidence of development of inhibitors in 395 previously untreated boys with severe haemophilia A following treatment with plasma-derived FVIII and two recombinant FVIII products, Kogenate Bayer and Advate (*22*). A total of 131, 137 and 127 boys were treated with plasma-derived FVIII, Advate and Kogenate Bayer, respectively). Clinically significant inhibitors were diagnosed in 121 patients. The cumulative incidences of inhibitors at 75 exposure days were 12.7% (plasma-derived FVIII), 20.4% (Advate) and 31.6% (Kogenate Bayer).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of haemophilia are not currently available.

The application presented a summary of consensus-based guidelines for the management of haemophilia from the World Federation of Hemophilia (*23*). Among the recommendations is one that states that the Federation does not express a preference for recombinant over plasma-derived clotting factor concentrates and that the choice between these classes of product must be made according to local criteria including availability, cost and patient preference. Additionally, for patients with severe haemophilia A or B in countries with health-care constraints, the guidelines include a strong recommendation for prophylaxis over episodic factor replacement therapy to reduce haemarthroses and other spontaneous and breakthrough bleedings and better preserve joint function.

Costs/cost–effectiveness

The cost–utility of haemophilia treatments varies based on the treatment approach, patient characteristics and disease severity (*8*).

Direct medical costs include the cost of medical treatments, health services, and surgical and medical supplies (*23*). Clotting factor concentrates for patients with severe haemophilia usually account for more than 90% of treatment-related costs (*24*). The medical and pharmaceutical costs of treating and preventing bleeding episodes in people with haemophilia have previously

been evaluated from various data sources (e.g. claims databases, surveys and chart reviews) and are substantial (*25*–*30*).

Alternative medicines to recombinant FVIII and FIX include plasma-derived coagulation factors, extended half-life recombinant FVIII and FIX, FVIII mimetics (e.g. emicizumab), anti-tissue-factor pathway inhibitors, rebalancing agents (e.g. concizumab and marstacimab) and gene therapy. The application stated that when standard half-life recombinant factors VIII and IX were first marketed in 1994 and 1997, respectively, the prices tended to be significantly higher per IU than prices for plasma-derived FVIII and FIX concentrates. Following the introduction of extended half-life recombinant FVIII and FIX concentrates, the prices of standard half-life recombinant products decreased, becoming competitive with plasma-derived concentrates. This trend continued with the introduction and availability of emicizumab.

The application included a summary of the global availability and prices of haemophilia treatments from unpublished data collected by the World Federation of Haemophilia (Table 9).

Table 9

Global availability and prices of haemophilia treatment products, by country income level, 2023–2024

Treatment	High-income countries		Upper middles-income countries		Low- and middle-income countries	
	No. (no. of products)	Price per IU, €	No. (no. of products)	Price per IU, €	No. (no. of products)	Price per IU, €
Emicizumab	8	15.12–108.50 (per mg)	5	13.00–52.32 (per mg)	3	39.00–77.00 (per mg)
pdFVIII	6 (8)	0.08–0.82	7 (13)	0.07–0.42	7 (12)	0.08–0.54
rFVIII	6 (19)	0.11–0.89	5 (9)	0.14–0.41	2 (2)	0.13–0.62
EHL FVIII	6 (19)	0.07–1.15	2 (3)	0.10–0.34	–	–
pdFIX	4 (7)	0.09–0.78	4 (5)	0.06–0.25	4 (4)	0.06–0.43
rFIX	2 (3)	0.75–0.87	1 (2)	0.36–0.37	–	–
EHL FIX	4 (9)	0.67–2.99	–	–	–	–
pdVWF	4 (8)	0.09–0.87	2 (4)	0.07–0.46	–	–

EHL: extended half-life; €: euro; FIX: factor IX; FVIII: factor VIII; pd: plasma-derived; VWF: von Willebrand disease; r: recombinant.
Source: Unpublished data from World Federation of Haemophilia Annual Global Survey 2023 and personal communication in 2024 (excludes the United States of America as an outlier).

A 2023 prospective study evaluated the cost–effectiveness of low- and intermediate-dose prophylaxis versus on-demand treatment in adults and children with moderate-to-severe haemophilia A from a societal perspective in India (*31*). Over a lifetime horizon, both low- and intermediate-dose prophylactic FVIII therapy were cost-effective for both adults and children compared with on-demand therapy at the patient level.

The high costs of managing haemophilia A were reported in a 2023 review of studies on health-care costs and resources use in the United States of America (*25*). Total yearly health-care costs ranged between 213 874 United States dollars (US$) and US$ 869 940 per patient and were largely driven by treatment choice, cost and intensity of prophylaxis therapy. The mean annual costs were between US$ 762 609 and US$ 831 702 for standard half-life recombinant FVIII, US$ 832 595 and US$ 1.1 million for extended half-life recombinant FVIII, and were US$ 693 709 for plasma-derived products and US$ 358 384 for emicizumab. Data from five studies showed that average yearly outpatient costs ranged between US$ 4772 and US$ 109 776, and costs associated with emergency department visits ranged between US$ 828 and US$ 3929. Data from six studies showed average inpatient costs of between US$ 12 336 and US$ 237 648. Additionally, parents of children with haemophilia A encountered higher health-service costs than control parents, and affected individuals faced considerable indirect costs, including productivity loss, costs for caregivers' unpaid time and patient disability.

Availability

Recombinant FVIII and FIX products are approved by regulatory agencies in high- and upper middle-income countries. Recombinant FVIII and FIX products that were approved between 1992 and 2004 are now off patent.

Multiple recombinant FVIII and FIX products are reported to be available globally.

There are multiple recombinant FVIII and recombinant FIX clotting factor concentrates approved and available on the market across all regions of the world. The application stated that 49/103 countries that reported FVIII use indicated having purchased recombinant products, and 36/92 countries that reported FIX use indicated having purchased recombinant products. In addition, more than 70 countries receive donations of treatment products, mostly recombinant clotting factor concentrates, from the World Federation of Haemophilia Humanitarian Aid Program each year.

Other considerations

Accurate diagnosis of haemophilia is essential to inform appropriate management. Genetic assessment, coagulation tests and factor assessments are used to

diagnose haemophilia, differentiate genotypes and predict the risk of inhibitor development. Haemophilia should be suspected in a male or female presenting with any of the clinical manifestations of haemophilia (such as spontaneous or injury-related bleeding, particularly in the joints and muscles; easy bruising and haematoma; excessive bleeding associated with medical procedures, surgery or trauma; mucosal bleeding (oral, nasal and genitourinary membranes); intracranial haemorrhage; gastrointestinal and abdominal bleeding; and central nervous system bleeds), and blood tests show normal platelet count, prolonged activated partial thromboplastin time, and normal prothrombin time (*9*).

The diagnosis of haemophilia is established by identification of decreased FVIII and FIX clotting activity and a normal, functional level of von Willebrand factor, and/or identification of an F8 or F9 gene variant by molecular genetic testing. A definitive haemophilia diagnosis is based on a factor assay to demonstrate deficiency of FVIII or FIX clotting activity. Occasionally, discrepancies in test results may occur. A standard one-stage factor assay shows near-normal or low-normal FVIII and FIX activity (40%-80%), whereas a two-stage chromogenic assay shows low FVIII and FIX activity therefore, low-normal in vitro clotting activity does not always exclude the presence of mild haemophilia (*9*).

Genetic assessment of haemophilia is important in defining disease biology, establishing diagnosis in difficult cases, predicting risk of inhibitor development, identifying female carriers, and providing prenatal diagnosis, if desired. Genotype analysis should be offered to all people with haemophilia and their at-risk female family members (*23*).

Committee recommendations

The Expert Committee recalled the request of the 2023 Expert Committee for an application to be sought for recombinant coagulation factors so that the available evidence for their comparative efficacy, safety and cost/cost–effectiveness could be fully evaluated.

The Committee recognized the importance of coagulation factor concentrates, both plasma-derived and recombinant, for patients with haemophilia.

The Committee considered that the evidence presented supported the effectiveness of recombinant factor VIII and recombinant factor IX being equal to plasma-derived coagulation factors for important outcomes including reduced bleeding rates, percentage of patients without bleeding events, improved joint health scores and improved health-related quality of life measurement scores. In terms of safety, the Committee noted that recombinant coagulation factors have virtually no risk of bloodborne virus transmission while plasma-derived coagulation factors undergoing multiple rigorous safety processes (e.g. donor screening, nucleic acid testing, viral inactivation/removal steps) have

an extraordinarily low (but not zero) risk of transmission of lipid-enveloped viruses. Overall, the Committee considered the balance of benefits to harms to be favourable.

The Committee noted that the prices of recombinant products has decreased over time and currently they are almost comparable with plasma-derived products. The Committee recognized that plasma-derived coagulation factors continue to represent an important treatment option and may offer advantages over recombinant products in the context of inhibitor development and may be more affordable in some settings.

Based on these considerations, the Expert Committee recommended the inclusion of recombinant coagulation factor VIII for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia A, and the inclusion of recombinant coagulation factor IX for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia B on the core list of the EML and EMLc.

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Section 12: Cardiovascular medicines

12.3 Antihypertensive medicines

Triple fixed-dose combinations of antihypertensive medicines – addition – EML

Valsartan + amlodipine + hydrochlorothiazide	**ATC code: C09DX01**
Perindopril + amlodipine + indapamide	**ATC code: C09BX01**

Proposal

Addition of triple fixed-dose combinations of antihypertensive medicines (including long-acting dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and thiazide or thiazide-like diuretics) to the WHO Model List of Essential Medicines (EML) for the treatment of essential hypertension in adults.

Applicant

The George Institute for Global Health

WHO technical department

The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The department supported the inclusion of triple fixed-dose combination antihypertensive on the EML. However, it highlighted the need to assess the implications of introducing these formulations for national procurement systems, including potential benefits from reduced logistics and inventory complexity versus the upfront costs of transitioning to a new medication. Consideration has to be given to negotiating bulk purchasing agreements, ensuring generic availability and integrating fixed-dose combinations into existing essential medicines lists to optimize affordability and sustainability within constrained health budgets. The department also considered that the inclusion of these formulations on the EML could catalyse wider adoption, stimulate competition to lower prices and enhance access in resource-constrained health systems.

EML/EMLc

EML

Section

12.3 Antihypertensive medicines

Dose form(s) & strengths(s)

Valsartan + amlodipine + hydrochlorothiazide

Solid oral dosage form: 160 mg + 5 mg + 12.5 mg, 160 mg + 5 mg + 25 mg, 160 mg + 10 mg + 12.5 mg, 160 mg + 10 mg + 25 mg, 320 mg + 10 mg + 25 mg

Perindopril + amlodipine + indapamide

Solid oral dosage form: 5 mg + 5 mg + 1.25 mg, 5 mg + 10 mg + 1.25 mg, 10 mg + 5 mg + 2.5 mg, 10 mg + 10 mg + 2.5 mg

Core/complementary

Core

Individual/square box listing

Square box, with therapeutic alternatives for individual component medicines consistent with those currently included in the EML.

Background

Triple fixed-dose combinations of antihypertensive medicines have not been previously evaluated for inclusion on the EML for the treatment of essential hypertension.

In 2019, the Expert Committee recommended the addition of four dual fixed-dose combinations (lisinopril + amlodipine, lisinopril + hydrochlorothiazide, telmisartan + amlodipine and telmisartan + hydrochlorothiazide) to the core list of the EML for the treatment of essential hypertension. Listing was recommended with square boxes for each component, indicating that other medicines within the respective pharmacological classes represent therapeutic alternatives. The Committee accepted the efficacy of fixed-dose combination antihypertensives compared with placebo or monotherapy for reducing blood pressure and cardiovascular events but expressed concern that the application did not provide strong evidence of the claimed advantages of fixed-dose combination therapy versus dual component monotherapy. However, the Committee accepted that many patients require multiple antihypertensive treatments to achieve blood pressure targets and recognized that fixed-dose combinations may confer advantages for patients over single medicines given concomitantly in terms of greater adherence and a reduced pill burden. The Committee considered that the ongoing availability of single-agent antihypertensive medicines was critical to allow treatment modification where necessary and that fixed-dose combinations should not displace single components at the country level. The Committee also noted that the availability of multiple fixed-dose combinations in varying strengths may be associated with significant supply chain and affordability issues in low- and middle-income countries. The Committee noted that the cost of fixed-

dose combinations varied in different settings and was not always the same as, or lower than, the sum of the cost of the corresponding component monotherapies. The Committee stressed that the cost of fixed-dose combinations should not be significantly higher than the sum of the cost of their component monotherapies and that the opportunity costs associated with treating patients with fixed-dose combinations must be considered, particularly in resource-constrained settings where access is limited (*1*).

Public health relevance

The public health relevance of effective treatments for hypertension is well established and accepted.

Hypertension, defined as blood pressure of 140/90 mmHg or higher, is an important global health issue, affecting about 1.4 billion people worldwide. Despite the availability of effective treatments, globally, only one in five individuals with hypertension has their blood pressure adequately controlled, with lower rates reported in low- and middle-income countries. Globally, about one in every three adults (aged 30–79 years) lives with hypertension. The prevalence of hypertension is greater than 25% in most countries, including low- and middle-income countries (*2*). Hypertension is a leading risk factor for cardiovascular diseases including heart attacks, strokes and heart failure (*3*).

Summary of evidence: benefits

Systematic reviews and meta-analyses

Triple versus dual combination therapy

The applicants conducted a systematic review and meta-analysis of 19 randomized controlled trials (16 322 participants) that compared triple versus dual combinations of antihypertensive medicines over 4 to 12 weeks. Outcome measures reported were systolic and diastolic blood pressure reduction and the proportion of patients achieving blood pressure control. Average baseline blood pressure was 162/99 mmHg in untreated patients and 150/94 mmHg in those uncontrolled on dual therapy. The results reported in the application found high-certainty evidence of significant reductions favouring triple combination therapy in systolic blood pressure (−5.4 mmHg (95% confidence interval (CI) −4.7 mmHg to −6.2 mmHg; $P < 0.001$; 18 randomized controlled trials, 14 372 participants), and diastolic blood pressure (−3.2 mmHg, 95% CI −2.6 mmHg to −3.7 mmHg; $P < 0.001$; 18 randomized controlled trials, 14 372 participants) and a greater proportion of participants achieving blood pressure control (66.8% versus 50.2%, rate ratio (RR) 1.3, 95% CI 1.2 to 1.4; $P < 0.001$; 13 randomized controlled trials, 11 274 participants).

Fixed-dose combination therapy versus free equivalent combination therapy

A 2021 systematic review and meta-analysis of 44 randomized and non-randomized studies assessed whether fixed-dose combination therapy improved adherence, persistence and blood pressure control compared with free equivalent combination therapy in patients with hypertension (4). A narrative analysis was performed for the outcomes of adherence and persistence, while a meta-analysis was done for blood pressure reductions. For adherence, 18/23 (78.3%) studies showed significantly improved adherence with fixed-dose combinations compared with free equivalent combination therapy. For persistence, 14/16 (87.5%) studies showed significantly improved persistence or lower discontinuation rates with fixed-dose combinations compared with free equivalent combination therapy. Fixed-dose combination therapy resulted in significant reductions in systolic (mean difference (MD) −3.99 mmHg, 95% CI −7.92 mmHg to −0.07 mmHg; $P = 0.05$) and diastolic blood pressure (MD −1.54mmHg, 95% CI −2.67 mmHg to −0.41 mmHg; $P = 0.0076$) compared with free equivalent combination therapy at week 12.

Low-dose combination therapy versus usual care

A 2023 systematic review and meta-analysis of seven randomized controlled trials (1918 participants) assessed the efficacy and safety of low-dose combination therapy consisting of three or four antihypertensive medicines compared to monotherapy, usual care or placebo (5). Pooled results for the primary outcome of mean reduction in systolic blood pressure showed significant differences favouring combination therapy at 4 to 12 weeks compared with active comparators (difference in means 7.4 mmHg, 95% CI 4.3 mmHg to 10.5 mmHg; $P < 0.001$; five randomized controlled trials) and placebo (difference in means 18.0 mmHg, 95% CI 15.1 mmHg to 20.8 mmHg; $P < 0.001$; four randomized controlled trials). Low-dose combination therapy was also associated with a greater reduction in systolic blood pressure at 6–12 months follow-up compared with active comparator (MD 6.4 mmHg, 95% CI 1.18 mmHg to 11.0 mmHg; $P = 0.06$; two randomized controlled trials). For the secondary outcome of the proportion of patients achieving blood pressure control (< 140/90 mmHg) at 4 to 12 weeks, pooled results significantly favoured combination therapy compared with active comparators (risk ratio (RR) 1.48, 95% CI 1.34 to 1.64; $P < 0.001$; five randomized controlled trials) and placebo (RR 3.03, 95% CI 1.93 to 4.77; $P < 0.001$; three randomized controlled trials).

Individual trials

Low-dose combination therapy versus usual care

The applicants identified four randomized controlled trials (1648 participants) that compared low-dose fixed-dose combination versus usual care in the

treatment of hypertension: TRIUMPH (6), QUARTET (7), QUARTET USA (8) and VERONICA (9). Upfront use of low-dose combination therapy achieved significantly greater reductions in systolic blood pressure than usual care at first to final follow up visit in TRIUMPH (MD at 6 months −9.8 mmHg, 95% CI −7.9 mmHg to −11.6 mmHg; $P < 0.001$), QUARTET (MD at 12 months −7.7 mmHg, 95% CI −5.2 mmHg to −10.3 mmHg; $P < 0.001$) and VERONICA (MD at 6 months −4.5 mmHg, 95% CI −0.09 mmHg to −8.1 mmHg; $P < 0.001$). In QUARTET USA, the reduction in systolic blood pressure favoured low-dose combination therapy but the difference was not significant (MD at 6 months −4.8 mmHg, 95% CI 1.3 mmHg to −10.8 mmHg; $P = 0.123$). The application reported that at final follow-up visit, blood pressure control (< 140/90 mmHg) was achieved in a greater proportion of participants receiving low-dose combination therapy than usual care (80% versus 65%, RR 1.22, 95% CI 1.14 to 1.30).

Triple versus dual combination therapy

An international, randomized, double-blind, active-controlled trial compared the efficacy and safety of a low-dose fixed-dose combination of telmisartan 20 mg + amlodipine 2.5 mg + indapamide 1.25 mg with each possible dual combination of its components (10). After a 4-week active run-in period, participants ($n = 1385$) were randomized 2:1:1:1 to continued half-dose fixed-dose combination, or half-dose telmisartan + amlodipine, or telmisartan + indapamide or amlodipine + indapamide. Doses were doubled at 6 weeks, except in cases of clinical contraindication. The primary efficacy outcome was the mean change in home systolic blood pressure from baseline to week 12. The results showed that at week 12, the difference in systolic blood pressure was significantly lower in the triple fixed-dose combination group than in each dual combination group with least-squares differences of: −2.5 mmHg (95% CI −3.7 mmHg to −1.3 mmHg) versus telmisartan + indapamide; −5.4 mmHg (95% CI −6.8 mmHg to −4.1 mmHg) versus telmisartan + amlodipine; and −4.4 mmHg (95% CI −5.8 mmHg to −3.1 mmHg) versus amlodipine + indapamide. Significant differences in home diastolic blood pressure, and clinical systolic and diastolic blood pressure favouring the triple fixed-dose combination group were also reported. Improvements in blood pressure control rates favouring the triple fixed-dose combination were also seen for all comparisons.

Summary of evidence: harms

From the systematic review performed by the applicants that compared triple versus dual combination antihypertensive therapy, there was low-certainty evidence of increased risks with triple combination therapy of any adverse event (46.8% versus 36.4%, RR 1.7, 95% CI 1.5 to 2.0; < 0.0001; 18 randomized controlled trials, 13 989 participants), and treatment-related adverse events (20.7% versus

15.3%, RR 1.7, 95% CI 1.4 to 1.9; $P < 0.0001$; 17 randomized controlled trials, 13 925 participants). There was very-low-certainty evidence of an increased risk of withdrawal due to adverse events associated with triple combination therapy (4.0% versus 3.0%, RR 1.4, 95% CI 1.2 to 1.7; $P < 0.0001$; 16 randomized controlled trials, 13 391 participants.

In the randomized controlled trial comparing low-dose fixed-dose combination of telmisartan 20 mg + amlodipine 2.5 mg + indapamide 1.25 mg with each possible dual combination of its components, withdrawal due to adverse events were not significantly different between treatment groups, occurring in 2.0%, 1.4%, 1.1% and 1.4% of participants in the triple combination, telmisartan + indapamide, telmisartan + amlodipine and amlodipine + indapamide groups, respectively. The proportions of participants with a serious adverse were 3.1%, 2.5% 2.1% and 2.2%, in the four treatment groups, respectively. The most commonly reported adverse events were generally mild and included dizziness and peripheral (*10*).

The application described predefined subgroup analyses of the TRIUMPH, QUARTET, QUARTET USA and VERONICA trials. No significant differences were reported between the low-dose combination and usual care groups in withdrawals due to adverse events, serious adverse events, dizziness or symptomatic hypotension, headache, musculoskeletal pain, gastrointestinal discomfort or peripheral oedema.

In the TRIUMPH trial, adverse events were reported in 38.1% and 34.8% of participants in the triple combination (telmisartan 20 mg + amlodipine 2.5 mg + chlorthalidone 12.5 mg) and usual care groups, respectively. The most commonly reported adverse events were musculoskeletal pain (6.0% and 8.0%, respectively) and dizziness, presyncope or syncope (5.2% and 2.8%, respectively). No significant differences were seen between treatment groups in withdrawals due to adverse events (6.6% versus 6.8%) (*6*). In the VERONICA trial, adverse events of special interest were reported in 2% and 3% of participants in the triple combination protocol group (quarter, half and standard doses of telmisartan + amlodipine + indapamide) and usual care groups, respectively. No discontinuations due to adverse events were reported in either group (*9*).

The 2023 systematic review reported that low-dose combination therapy was associated with higher rates of dizziness compared with active comparators (14% versus 11%, RR 1.28, 95% CI 1.00 to 1.63) but not for peripheral oedema, headache, musculoskeletal pain or serious adverse events. No significant difference was seen between treatment groups for withdrawals due to adverse events (5% versus 4%, RR 1.14, 95% CI 0.71 to 1.82) (*5*).

Additional evidence

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WHO guidelines

The 2021 WHO guidelines for the pharmacological treatment of hypertension in adults includes a strong recommendation for the use of thiazide and thiazide-like diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, or long-acting dihydropyridine calcium channel blockers as initial treatment for adults with hypertension requiring pharmacological treatment (high-certainty evidence). The guidelines also include a conditional recommendation for combination therapy, preferably with a single-pill combination (to improve adherence and persistence) as initial treatment in adults with hypertension requiring pharmacological treatment and they recommend that the medicines used in combination be chosen from the above-mentioned medicine classes (moderate-certainty evidence) (*3*).

Costs/cost–effectiveness

A cost analysis from the India Hypertension Control Initiative showed that the procurement prices of fixed-dose combinations are comparable to those of individual pills in the public sector (*11*).

A 2020 study compared prices of antihypertensive fixed-dose combinations and single component pills in equivalent doses in the private health-care sector in India (*12*). Three triple fixed-dose combinations were included in the analysis (two with different doses of amlodipine + telmisartan + hydrochlorothiazide and one with amlodipine + olmesartan + hydrochlorothiazide). Prices for the fixed-dose combinations were consistently higher than the sums of their components.

In a report developed by Resolve to Save Lives in collaboration with the Médecins Sans Frontières Access Campaign to identify barriers to affordable antihypertensive medicines in low- and middle-income countries, fixed-dose combinations were cheaper than the separate agent equivalents in the private sector in countries with larger domestic manufacturing capacity, i.e. Brazil, Philippines and South Africa. However, the reverse was true for countries with smaller domestic pharmaceutical market, such as Lebanon and Nigeria (*13*)

The application presented a summary of retail prices of the proposed fixed-dose combinations in private markets in India, Kenya, Nigeria and Philippines. Prices showed considerable variability by country. For example, 1 months' supply of valsartan 160 mg + amlodipine 10 mg + hydrochlorothiazide 12.5 mg was 3.61 United States dollars (US$) in India, US$ 37.30 in Kenya, US$ 28.86 in Nigeria and US$ 13.80 in Philippines.

A 2019 study conducted a within-trial (6 month) and modelled (10 year) economic evaluation of the TRIUMPH from the Sri Lankan health-system perspective (*14*). Incremental cost-effectiveness ratios were calculated to estimate the cost per additional participant achieving target blood pressure at 6 months and cost per disability adjusted life year (DALY) averted over 10 years. Using a

fixed-dose combination cost of US$ 0.16 per day based on the price of a fixed-dose combination for hypertension in India, the study reported a cost per participant reaching target blood pressure at 6 months of US$ 7.93 (95% CI US$ 6.59 to 11.84) and an incremental cost-effectiveness ratio of US$ 2842.79 (95% CI US$ −28.67 to 7514.24) per DALY averted over 10 years. In sensitivity analyses, incremental cost-effectiveness ratios were most sensitive to the price of the fixed-dose combination. The fixed-dose combination strategy was considered likely to be cost-effective at willingness-to-pay thresholds ≥ US$ 6100 per DALY averted.

A 2011 meta-analysis of 12 retrospective database studies compared health-care resource use costs, adherence and persistence between groups of patients taking antihypertensive medicines as fixed-dose combinations versus free-equivalent components (*15*). Pooled analysis of annual health-care costs reported significantly lower costs for fixed-dose combinations (mean difference US$ −1357.01, 95% CI US$ −1935.49 to −778.53; seven studies, 44 336 participants).

A 2013 retrospective cost analysis evaluated the economic impact of switching to fixed-dose combination antihypertensive therapy from angiotensin-receptor blocker-based antihypertensive treatment using pharmacy claims data in Japan (*16*). The study reported that switching to fixed-dose combination treatment was associated with an annual saving of US$ 112.00 for patients in their costs for antihypertensive medicines. However, it was noted that in about 20% of patients who switched from angiotensin-receptor blocker monotherapy to fixed-dose combination therapy, the medicine costs increased by US$ 25.50.

A 2009 study estimated the potential cost-savings from switching patients from angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and thiazide diuretic antihypertensive treatment as separate agents to fixed-dose combination treatment from the health-system perspective in Canada (*17*). Based on a conversion of 60–100% of patients to fixed-dose combination products, the estimated potential cost savings were Canadian$ 27 to 45 million a year.

Availability

The application provide a summary of a sample of countries/regions in which valsartan + amlodipiine + hydrochlorothiazide, perindopril + amlodipine + indapamide, and olmesartan + amlodipine + hydrochlorothiazide products are available. The fixed-dose combinations are variably available in Argentina, Australia, Europe, India, Kenya, Mexico, Nigeria, Philippines and the United States of America. It was reported that telmisartan + amlodipine + indapamide is not currently available in any country; however, regulatory applications are under review or planned for 2025 in different settings.

Other considerations

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Committee recommendations

The Expert Committee acknowledged the substantial global burden of hypertension and its role as a major risk factor for cardiovascular disease. The Committee also acknowledged the role of combination therapy, using either multiple single agent antihypertensives or fixed-dose combinations, in the management of hypertension, as recommended in WHO guidelines.

The Committee noted the benefits of triple combination antihypertensive therapy for reductions in systolic and diastolic blood pressure and some evidence of improved adherence and persistence compared with free equivalent combination therapy. Adverse effects are generally mild and manageable, and consistent with the known adverse event profiles of the components.

Based on these considerations, the Expert Committee recommended the inclusion of triple fixed-dose combination antihypertensive formulations containing a long-acting dihydropyridine calcium channel blocker, an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, and a thiazide or thiazide-like diuretic on the core list of the EML based on a favourable balance of benefits to harms. Listing is recommended for valsartan + amlodipine + hydrochlorothiazide and perindopril + amlodipine + indapamide, with each component with a square box, indicating that other medicines within the respective pharmacological classes represent therapeutic alternatives for national selection. The Committee emphasized that triple fixed-dose combinations are intended to complement the antihypertensive options already included in the Model List, such as monotherapies and dual combinations. Their inclusion aims to expand treatment choices in countries that have the capacity to manage antihypertensive medicines through robust supply chains, procurement systems and national guidelines, which define the appropriate use of different classes and their combinations. The Committee noted that these formulations do not represent new medicines, but rather combinations of active pharmaceutical ingredients already recommended in the Model List.

The Committee noted that cost comparisons of fixed-dose combinations with the sum of the component monotherapies varied across settings and stressed the need for national decision-makers to take favourable differential price into consideration when making national selection decisions. The Committee also reiterated the importance of the continued availability of single-agent antihypertensives to allow the provision of monotherapy when indicated and treatment modification when required.

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Section 13: Dermatological medicines

13.1 Antifungal medicines

Ciclopirox hydroxypropyl chitosan – addition – EML

Ciclopirox hydroxypropyl chitosan **ATC code: D01AE14**

Proposal

Addition of ciclopirox 8% hydroxypropyl chitosan (HPCH) nail hydrolacquer to the core list of the EML for the treatment of onychomycosis in adults.

Applicant

Almirall S.A., Barcelona, Spain

WHO technical department

The Control and Response Strategies unit within the Antimicrobial Resistance Division reviewed and provided comments on the application. The technical unit did not support the inclusion of ciclopirox HPCH on the EML due to insufficient evidence. The technical unit also noted the need for a more comprehensive review of all available topical and systemic treatments for onychomycosis. However, in the context of competing priorities, the unit did not consider that such a review was a high priority at this time.

EML/EMLc

EML

Section

13.1 Antifungal medicines

Dose form(s) & strengths(s)

Solution: 80 mg/g

Core/complementary

Core

Individual/square box listing

Individual

Background

Ciclopirox has not been previously evaluated for inclusion on the EML.

The EML currently includes systemic and topical antifungals for other indications.

Public health relevance

Onychomycosis is a broad descriptor for fungal infections of the nail that are caused by dermatophytes, yeasts and saprophytic moulds. Onychomycosis caused by dermatophytes are responsible for about 60–70% of all infections, while yeasts account for about 20% (*1*). Onychomycosis is a progressive but not life-threatening disease. The global prevalence of onychomycosis has been reported at around 10% (*2*), but it may be as high as 48% in some settings (*3*). Prevalence increases with age, reaching over 50% in adults 70 years or older (*4*).

Onychomycosis often presents with nail discolouration, separation, brittleness or thickening that typically worsens with time. These clinical signs may cause localized pain and social embarrassment and contribute to negative quality of life (*5*).

Onychomycosis is often difficult to treat and is associated with high rates of treatment failure and recurrence. Systemic treatment with oral antifungals requires prolonged treatment and is also associated with relatively low cure rates (*1*).

Summary of evidence: benefits

Ciclopirox has antimicotic activity against dermatophytes, yeasts and non-dermatophyte moulds. It may be fungistatic or fungicidal depending on concentration and duration of contact with target organisms. It also has antibacterial activity against gram-positive, gram-negative aerobic and anaerobic bacteria (*6*).

HPCH is a formulation technology to increase the permeation of ciclopirox into the nails (*7*).

Systematic reviews and meta-analyses

A 2020 Cochrane systematic review of 56 randomized controlled trials (12 501 participants) assessed the clinical and mycological effects of topical and device-based therapies for toenail onychomycosis in adults (*8*). Most studies were between 48 and 52 weeks in duration and were conducted in the outpatient setting. The review included studies of both ciclopirox 8% HPCH hydrolacquer and ciclopirox water insoluble lacquer. The primary efficacy outcome of the review was complete cure rate, defined as the proportion of participants with 0% nail plate involvement and mycological cure at follow-up. For the comparison of ciclopirox 8% HPCH hydrolacquer versus active comparators (ciclopirox 8% water

insoluble lacquer or amorolfine 5% lacquer; two randomized controlled trials, 490 participants), the review found moderate-quality evidence that ciclopirox 8% HPCH hydrolacquer would probably lead to complete cure compared with the comparators (12.8% versus 5.2%, risk ratio (RR) 2.43, 95% confidence interval (CI) 1.32 to 4.48). For the comparison of ciclopirox 8% water insoluble lacquer versus vehicle (two randomized controlled trials, 460 participants), the review found low-quality evidence that ciclopirox may lead to complete cure compared with vehicle (6.9% versus 0.4%, RR 9.29, 95% CI 1.72 to 50.14).

A 2015 network meta-analysis of 19 randomized controlled trials (5551 participants) evaluated the relative efficacy of different treatments for onychomycosis (*9*). The trials had a parallel-group design and a study duration of at least 48 weeks. The treatments analysed included: oral itraconazole, fluconazole and terbinafine; topical ciclopirox 8% water-insoluble and amorolfine lacquers; and topical terbinafine, tavaborole and efinaconazole nail solutions. All treatments were significantly superior to placebo for mycological cure, the most effective being oral terbinafine 250 mg (odds ratio (OR) 46.72, 95% CI 24.38 to 101.34) and pulse itraconazole 400 mg (OR 18.36, 95% CI 6.14 to 63.33). The OR for ciclopirox 8% water-insoluble lacquer was 4.25 (95% CI 2.25 to 8.12). No significant differences were seen between ciclopirox 8% water-insoluble lacquer and other topical treatments for mycological cure; however, point estimates favoured ciclopirox in comparisons with amorolfine lacquer (OR 1.09, 95% CI 0.31 to 3.61) and terbinafine nail solution (OR 1.04, 95% CI 0.36 to 2.92). All oral treatment were significantly superior to topical treatments.

Randomized trials

A 2009 company-sponsored multicentre, randomized, three-arm, trial evaluated the efficacy and safety of ciclopirox 8% HPCH hydrolacquer versus ciclopirox 8% water insoluble lacquer and placebo in 467 patients with onychomycosis (24–100% nail involvement) (*10*). Patients were randomized 2:2:1 to receive 48 weeks of treatment (daily application), followed by a 12-week follow-up period. The primary endpoint was complete cure, defined as conversion to negative of both potassium hydroxide microscopy and fungal culture, and 100% growth of healthy nail at week 48 and week 52. The complete cure rate was 5.7%, 3.2% and 0% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. During the treatment period, ciclopirox 8% HPCH was found to be superior to placebo and non-inferior to ciclopirox 8% water insoluble lacquer. At the end of the follow-up period, ciclopirox 8% HPCH was clinically and statistically superior to ciclopirox 8% water insoluble lacquer (12.7% versus 5.8%; $P < 0.05$). Response rates at 48 weeks were 24%, 17.3% and 6.4% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively.

A post hoc analysis of the above-mentioned trial, evaluated the efficacy of ciclopirox 8% HPCH in the subset of 302 patients with mild to moderate onychomycosis (≤ 50% nail involvement) (*11*). Complete cure rates after 48 weeks were 7.6%, 3.3% and 0% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. After 60 weeks, the corresponding complete cure rates were 15.1%, 5.8% and 1.6%. Response rates at 48 weeks were 31.9%, 24.2% and 9.5% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. Ciclopirox 8% HPCH was significantly superior to placebo at week 48 ($P = 0.001$), however the difference at week 60 was not significant ($P = 0.052$).

A 2015 company-sponsored randomized, controlled, parallel-group clinical trial compared the effectiveness and safety of ciclopirox 8% HPCH hydrolacquer and amorolfine 5% lacquer in 120 patients with mild to moderate toenail onychomycosis (*12*). Patients were randomized 1:1 to receive daily application of ciclopirox 8% HPCH hydrolacquer or twice weekly application of amorolfine 5% lacquer. Primary efficacy outcomes were complete cure rate, treatment success, and mycological cure, evaluated at different times up to 48 weeks in the intention-to-treat population. Ciclopirox 8% HPCH was significantly superior to amorolfine 5% for complete cure rate at week 48 (35.0% versus 11.7%; $P < 0.001$). The difference in cure rate between treatments was not significant at week 24. At week 48, ciclopirox 8% HPCH was also significantly superior to amorolfine 5% for the outcomes of treatment success (58.3% versus 26.7%; $P < 0.001$) and mycological cure (100% versus 81.7%; $P < 0.001$). Numbers-needed to treat for complete cure were computed as 3 and 11 for ciclopirox and amorolfine, respectively.

A 2015 non-interventional study in Germany evaluated the effectiveness of ciclopirox HPCH hydrolacquer in 70 patients on whom prior treatment with amorolfine lacquer had failed (*13*). The primary outcome was the conversion to negative mycological findings (potassium hydroxide test and culture) at 24 weeks. For the primary outcome, response rates for treatment success and treatment failure with ciclopirox 8% HPCH in the full analysis set were 58.6% and 41.4%, respectively.

Summary of evidence: harms

In the 2020 Cochrane systematic review there was low-quality evidence of an increased risk of adverse events associated with ciclopirox 8% water-insoluble lacquer than vehicle (11.3% versus 7%, RR 1.61, 95% CI 0.89 to 2.92; two randomized controlled trials, 460 participants). The most commonly reported adverse events were application-site reactions (transient tingling, burning, or pain with treatment use), rashes (mild erythema in the skin surrounding the nail) and alterations in nail colour or shape. The risk of adverse events was similar between for ciclopirox

8% HPCH hydrolacquer and active comparators (ciclopirox 8% water-insoluble lacquer and amorolfine 5%: 6.3% versus 12.1%; RR 0.60, 95% CI 0.19 to 1.92; two randomized controlled trials, 487 participants, low quality of evidence) (*8*).

From the 2009 trial of ciclopirox 8% HPCH hydrolacquer versus ciclopirox 8% water insoluble lacquer and placebo, no serious or severe adverse events were reported in any treatment arm. Local application-site signs and symptoms such as itching, burning, pain, erythema or oedema were all mild-to-moderate and less frequent with ciclopirox 8% HPCH than with ciclopirox 8% water insoluble lacquer (*10*).

Additional evidence

A 2020 systematic review and network meta-analysis evaluated the effectiveness and safety of monotherapy and combination treatments for toenail onychomycosis (*14*). Of 75 records meeting the inclusion criteria for the quantitative analysis, only 26 (8136 participants, 31 trials) met the criteria for network meta-analysis reporting mycological cure rates or adverse events. Treatments in the evidence network were ciclopirox 8% water insoluble lacquer, efinaconazole 10% topical solution, oral fluconazole, oral itraconazole, oral terbinafine and tavaborole 5% solution. Amorolfine, ciclopirox 8% HPCH hydrolacquer, griseofulvin, devised-based therapies and combination therapies were unable to be included in the network. All treatments were significantly superior to placebo for mycological cure, the most effective being continuous itraconazole 200 mg (OR 18.61, 95% CI 7.40 to 46.81) and continuous terbinafine 250 mg (OR 16.41, 95% CI 6.49 to 41.47). The OR for ciclopirox 8% water insoluble lacquer was 4.11 (95% CI 2.21 to 7.64). Ciclopirox 8% water insoluble lacquer was not significantly different from other topical treatments, pulse terbinafine 500 mg, pulse itraconazole 400 mg or fluconazole for mycological cure. Topical treatments had the lowest surface under the cumulative ranking curve (SUCRA) scores of all treatments evaluated. With the exception of efinaconazole 10%, for which more transient application-site reactions were reported, the risk of adverse events with any of the treatments were not significantly different from placebo.

WHO guidelines

WHO guidelines for the treatment of onychomycosis are not currently available.

The 2024 edition of the Pan American Health Organization's guide for the treatment of infectious diseases (*15*) includes the following oral treatment recommendations for onychomycosis in adults:

Fingernails

- First choice: terbinafine 250 mg a day or 500 mg a day for 1 week every month, for 6–8 weeks;

- Other options: itraconazole 200 mg a day for 3 months or 200 mg twice daily for 1 week every month for 2 months; fluconazole 300–450 mg once weekly for 3–6 months.

Toenails

- First choice: terbinafine 250 mg a day for 3–4 months;
- Other options: itraconazole 200 mg a day for 3 months or 200 mg twice daily for 1 week every month for 3–4 months; fluconazole 300–450 mg once weekly for 6–12 months.

The application reported that topical ciclopirox (both HPCH hydrolacquer and water insoluble lacquer) is recommended by numerous international and national guidelines and other scientific articles.

Costs/cost–effectiveness

No studies evaluating the cost or cost-effectiveness of ciclopirox 8% HPCH hydrolacquer were identified in the literature search conducted for the purpose of the application.

The application reported publicly available prices for ciclopirox 8% HPCH in 20 of the 39 markets in which it is available. Prices ranged from 9.44 United States dollars (US$) (France) to US$ 35.40 (Switzerland) for 3.3 mL and from US$ 16.42 (France) to US$ 47.40 (Finland) for 6.6 mL.

Availability

The application reported that ciclopirox 8% HPCH has regulatory approval and market availability in 39 countries globally. Ciclopirox 8% water-insoluble lacquer has regulatory approval and market availability in 33 countries globally. In many of these countries, it is available as an over-the-counter product.

Other considerations

Resistance to oral antifungals is increasing, with resistant yeast and mould species associated with systemic infections categorized by WHO as fungal pathogens posing a significant threat to public health (*16*). Resistant strains prolong disease duration, increasing the opportunity for disease transmission, thereby increasing infection rates and encouraging disease spread (*17*).

A 2024 review discussed the role of antifungal stewardship and topical antifungals in the treatment of onychomycosis (*17*). The review noted that no natural dermatophyte resistance to topical antifungals has been reported, suggesting no liability to induce dermatophyte resistance as validated by in vitro studies. Ciclopirox has also been noted for its effectiveness against terbinafine- and azole-resistant fungal species. It was also noted that combination topical

and oral antifungal treatment may reduce treatment failure caused by primary resistance and limit the development of a secondary resistance while also improving treatment adherence.

In contrast to other topical antifungals for onychomycosis that target the ergosterol synthesis pathway, ciclopirox has a unique mechanism of action against which the pathogen is unable to adapt by mutating the binding site of the targeted enzyme. Specifically, it is distinguished from therapeutic alternatives due to its chelation of polyvalent metal cations, leading to the inhibition of many cellular activities and modifications to the fungal plasma membrane. This mechanism is indicative of a lower propensity for inducing antifungal resistance in the species that contribute to onychomycosis. An important factor in preventing the development of resistance is the ability of medicines with fungicidal activities to permeate the nail and reach the site of infection. In this regard, in vitro studies have shown that the permeability of ciclopirox 8% HPCH hydrolacquer is about 10 times greater than that of efinaconazole and significantly improved relative to ciclopirox water insoluble lacquer (*18*). It has been hypothesized that these results were also attributable to the ability of ciclopirox to accumulate in the nail, enabling gradual release into both the nail plate and nail bed. Similarly, in contrast to terbinafine, itraconazole and amorolfine, where resistant strains were identified in vitro, no mutant resistance to ciclopirox was identified in *Trichophyton rubrum* strains (*19*).

Committee recommendations

The Expert Committee acknowledged that onychomycosis, despite its non-life-threatening nature, can cause localized pain and social embarrassment, and negatively affect quality of life. It is often difficult to treat, with treatment duration being lengthy and associated with high rates of failure, poor adherence and increased risk of relapse.

In consideration of the evidence presented in the application, the Committee noted that while topical application of ciclopirox 8% hydroxypropyl chitosan demonstrated broad-spectrum antifungal activity, complete cure rates remained low (about 15% or less). The Committee noted that ciclopirox has limited efficacy in severe cases of onychomycosis, especially when the nail matrix is involved. The safety profile was generally favourable, with mild and localized adverse events such as nail discolouration. However, no evidence from head-to-head trials with oral or combined oral and topical antifungal treatments were presented, nor were any comparative cost–effectiveness studies.

Therefore, the Expert Committee did not recommend the inclusion of ciclopirox hydroxypropyl chitosan nail hydrolacquer on the EML for the treatment of onychomycosis in adults because of the lack of robust evidence of comparative benefits and safety versus oral or combined oral and topical antifungal treatments, and unknown comparative cost–effectiveness.

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13.4 Medicines affecting skin differentiation and proliferation

Adalimumab – new indication – EML and EMLc

Adalimumab **ATC code: L04AB04**

Proposal

Extension of the indications for adalimumab on the complementary list of the EML and EMLc to include the treatment of adults and children with moderate-to-severe psoriasis. Listing is requested for adalimumab as the representative tumour necrosis factor (TNF) alpha inhibitor, with certolizumab pegol, etanercept and infliximab as specified therapeutic alternatives.

Applicant

International League of Dermatological Societies

WHO technical department

Department of Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

13.4 Medicines affecting skin differentiation and proliferation

Dose form(s) & strengths(s)

EML

Injection (subcutaneous): 40 mg/0.4 mL, 40 mg/0.8 mL, 80 mg/0.8 mL in prefilled pen and prefilled syringe

EMLc

Injection (subcutaneous): 40 mg/0.4 mL, 40 mg/0.8 mL in prefilled pen; 20 mg/0.2 mL, 40 mg/0.4 mL, 40 mg/0.8 mL in prefilled syringe; 40 mg/0.8 mL in vial

Core/complementary

Complementary

Individual/square box listing

Square box for adalimumab, with certolizumab pegol, etanercept and infliximab as specified therapeutic alternatives.

Background

Adalimumab (and alternative TNF-alpha inhibitors) have not previously been evaluated for inclusion on the Model Lists for use in the treatment of moderate-to-severe psoriasis.

In 2019, adalimumab (as the representative TNF-alpha inhibitor) was added to the complementary list of the EML and EMLc for second-line treatment of severe chronic inflammatory autoimmune disorders (ankylosing spondylitis, Crohn disease , juvenile idiopathic arthritis and rheumatoid arthritis) on the basis of a favourable benefit-to-harm profile (*1*).

In 2023, the Expert Committee recommended the addition of oral methotrexate on the complementary list of the EML and EMLc for second-line treatment of patients with psoriasis, given evidence of the favourable balance of desirable to undesirable effects (*2*). Before 2023, only topical therapies (coal tar, corticosteroids, salicylic acid and vitamin D analogues) were included on the Model Lists for treatment of psoriasis.

Public health relevance

The public health relevance of effective treatments for psoriasis has been accepted previously by the Expert Committee.

Data for 2021 from the Global Burden of Disease study report a global prevalence of psoriasis of almost 53 million people and an annual global incidence of nearly 6 million. Psoriasis was responsible for 0.13% of global disability-adjusted life years in 2021. The prevalence was highest in the WHO Western Pacific Region and lowest in the African Region and Eastern Mediterranean Region. At the country level, the prevalence was highest in high- and middle-income countries and lowest in low-income countries (*3*).

In children, the typical age at onset of paediatric psoriasis is between 8 and 11 years (*4*, *5*).

Patients with psoriasis have a reduced quality of life that is similar to or worse than those with other chronic diseases (*6*, *7*). Studies have reported that patients with psoriasis also have a higher risk of death compared with individuals without the disease (*8*–*10*).

In a 2020 consensus statement from the International Psoriasis Council, patients with psoriasis are candidates for systemic therapy if they meet one or more of the following criteria: the disease affects > 10% of the body surface area; the disease involves special body areas (face, palms, soles, genitalia, scalp or nails); and topical therapy has failed for the patient (*11*).

Treatment of psoriasis usually extends over the life of the patient and can involve topical therapies, systemic therapies and phototherapy, used either individually or in combination.

Summary of evidence: benefits

Short-term efficacy studies (up to 24 weeks)

A 2023 Cochrane living systematic review and network meta-analysis of 179 randomized controlled trials (62 339 participants) compared benefits and harms of non-biological systemic agents, small molecules and biologics in adults older than 18 years with moderate-to-severe plaque psoriasis. The review provided a ranking of treatments according to their benefits and harms (*12*). The included trials compared systemic treatments with placebo or active comparators. Patients had an average age of 44.6 years and a mean baseline Psoriasis Area and Severity Index (PASI) score of 20.4. The primary efficacy outcome was the proportion of participants who achieved clear or almost clear skin (PASI 90) at induction phase (8 to 24 weeks after randomization). Secondary efficacy outcomes included the proportion of participants who achieved PASI 75, and the proportion of participants who achieved a physician global assessment value of 0 or 1 at induction phase.

All interventions were superior to placebo for achieving PASI 90, with the most effective treatment being infliximab (risk ratio (RR) 49.16, 95% confidence interval (CI) 20.49 to 117.96; high-certainty evidence). In absolute terms, 934 more patients per 1000 would achieve PASI ≥ 90. For the other TNF-alpha inhibitors proposed in the application, results versus placebo were: adalimumab RR 16.13 (95% CI 13.65 to 19.06; high-certainty evidence); certolizumab pegol RR 12.16 (95% CI 8.87 to 16.68; moderate-certainty evidence); and etanercept RR 9.66 (95% CI 8.14 to 11.48; moderate-certainty evidence). In absolute terms, these results correspond to 306, 234 and 184 more patients per 1000 achieving PASI ≥ 90, respectively (*12*).

For achieving PASI 90, infliximab was significantly superior to adalimumab (RR 3.05, 95% CI 1.26 to 7.40; high-certainty evidence), certolizumab pegol (RR 4.04, 95% CI 1.60 to 10.19; moderate-certainty evidence) and etanercept (RR 5.09, 95% CI 2.10 to 12.33; moderate-certainty evidence). Adalimumab was significantly superior to etanercept (RR 1.67, 95% CI 1.47 to 1.89; moderate-certainty evidence). No significant difference was found between adalimumab and certolizumab pegol (RR 1.33, 95% CI 0.98 to 1.79; moderate-certainty evidence) (*12*).

In comparisons of TNF-alpha inhibitors with interleukin (IL) 12/23 and 23 inhibitors, infliximab was significantly superior to ustekinumab (RR 2.84, 95% CI 1.17 to 6.87; moderate-certainty evidence) and tildrakizumab (RR 2.89, 95% CI 1.16 to 7.20; high-certainty evidence). Ustekinumab was significantly superior to certolizumab pegol (RR 1.43, 95% CI 1.06 to 1.91) and etanercept (RR 1.79, 95% CI 1.60 to 2.01) (both moderate-certainty evidence). No significant difference was seen between ustekinumab and adalimumab

(RR 1.07, 95% CI 0.98 to 1.18; moderate-certainty evidence). IL 23 inhibitors risankizumab and guselkumab were significantly superior to ustekinumab and all TNF-alpha inhibitors except infliximab. Surface under the cumulative ranking curve (SUCRA) rankings versus placebo for PASI 90 were: infliximab (first), risankizumab (fourth), guselkumab (eighth), ustekinumab (ninth), tildrakizumab (10th), adalimumab (11th), certolizumab (13th) and etanercept (15th). Results for the secondary efficacy outcomes of PASI 75 and physician global assessment 0/1 were similar to the results for PASI 90 (*12*).

Long-term efficacy and safety studies

The applicants searched the literature to identify long-term efficacy/effectiveness and safety studies on the use of adalimumab and/or ustekinumab in patients with psoriasis and identified multiple eligible studies (*13*–*38*), which were briefly summarized in Appendix 8.1 of the application. Results from selected systematic reviews and network meta-analyses are summarized below.

A 2021 network meta-analysis of 14 randomized controlled trials compared efficacy (measured as PASI 75/90/100) outcomes of treatments for moderate-to-severe plaque psoriasis in adults (*13*). The study included regimens for IL-12/23, IL-23, IL-17 and TNF-alpha inhibitors given for 48 to 56 weeks after randomization. No risk-of-bias assessment was conducted. The proportions of participants who achieved a PASI 90 response were: 84.9% for risankizumab; 81.3% or 79.4% for bimekizumab (depending on regimen); 78.6% for brodalumab; 77.3% for guselkumab; 72.0% for ixekizumab; 66.2% for secukinumab; 55.1% for ustekinumab; 50.8% for adalimumab; and 37.4% for etanercept. Risankizumab, bimekizumab, brodalumab, guselkumab, ixekizumab and secukinumab significantly outperformed adalimumab for this outcome, whereas adalimumab was superior to etanercept.

A 2022 systematic review and network meta-analysis also evaluated PASI response at 1 year of targeted therapies for moderate-to-severe plaque psoriasis in adults (*36*). Nine randomized controlled trials comparing eight interventions (adalimumab, brodalumab, etanercept, guselkumab, ixekizumab, risankizumab, secukinumab and ustekinumab) were included in the primary efficacy analysis. Results showed that IL-17 and IL-23 inhibitors outperformed other biological therapies for achieving PASI outcomes. In a secondary analysis of 28 randomized controlled trials, including data for apremilast, certolizumab pegol and infliximab, all therapies significantly outperformed placebo. No significant differences were seen in PASI 90 between infliximab and adalimumab (median RR 1.11, 95% CI 0.82 to 1.60), and certolizumab pegol (400 mg) and adalimumab (median RR 1.05, 95% CI 0.70 to 1.52). Both adalimumab and ustekinumab outperformed etanercept (median RR 1.30, 95% CI 1.05 to 1.78 for adalimumab and median RR 1.38, 95% CI 1.12 to 1.92 for ustekinumab).

Paediatric patients

A company-funded randomized, parallel group, double-blind phase III trial compared adalimumab and oral methotrexate in 114 children aged 4 to 18 years with psoriasis not responsive to topical treatment (*39*). Patients were randomized to receive adalimumab 0.8 mg/kg ($n = 38$), adalimumab 0.4 mg/kg ($n = 39$) or methotrexate ($n = 37$). Primary efficacy endpoints were the proportions of patients achieving PASI 75 and physician global assessment 0/1 at week 16. A significant difference was found favouring adalimumab 0.8 mg/kg over methotrexate in the proportion of patients who achieved PASI 75 (57.9% versus 32.4%; $P = 0.027$) but not physician global assessment 0/1 (60.5% versus 40.5%; $P = 0.08$). PASI 75 and physician global assessment 0/1 responses were reported in 43.6% and 41.0%, respectively, of patients in the adalimumab 0.4 mg/kg group.

Observational studies

The application presented summaries of several observational studies that support longer-term efficacy and quality-of-life outcomes of adalimumab (*40*–*46*).

Summary of evidence: harms

In the 2023 Cochrane living systematic review and network meta-analysis, the primary safety outcome was the proportion of participants with serious adverse events (death, life-threatening events, initial or prolonged hospitalizations and adverse events requiring intervention to prevent permanent impairment or damage) at the induction phase (*12*). No significant differences were seen between active interventions versus placebo in the risk of serious adverse events. Considering TNF-alpha inhibitors IL-12-23 and IL-23 inhibitors SUCRA rankings versus placebo for serious adverse events were: risankizumab (third), certolizumab (fifth), etanercept (sixth), tildrakizumab (eighth), guselkumab (11th), ustekinumab (13th), adalimumab (14th) and infliximab (19th).

In the 2023 network meta-analysis, rates of adverse events for the various treatments investigated were 37.5% for risankizumab, 72.2% for guselkumab, 72.9% for adalimumab, 76.6% for secukinumab, 76.9% for ustekinumab, 80.9% for ixekizumab and 82.3% for bimekizumab (*13*). Risankizumab had a significantly lower rate of adverse events than secukinumab, ustekinumab and bimekizumab. Rates of serious adverse events at week 48–56 were 4.4% for risankizumab, 5.4% for adalimumab, 5.7% for ustekinumab, 5.9% for guselkumab, 6.9% for secukinumab, 7.2% for bimekizumab and 10.5% for ixekizumab. No significant difference was seen between treatments for serious adverse events.

Treatment with TNF-alpha inhibitors has been associated with an increased risk of serious infections. Real-world registry data studies have reported a higher risk with adalimumab and infliximab compared with non-methotrexate and non-biologic therapies (*25*), but no increased risk compared to methotrexate

or other biologic therapies (*19*, *37*). TNF-alpha inhibitor treatment has also been associated with an increased risk of reactivation of latent tuberculosis (*17*, *32*).

Treatment with TNF-alpha inhibitors has also been associated with a slightly increased long-term risk of malignancy, particularly non-melanoma skin cancer in patients with psoriasis compared with non-biologic therapy. However, the evidence is mixed with some studies showing an elevated risk (*22*, *31*), and others showing no association (*29*).

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of psoriasis are not currently available.

Costs/cost–effectiveness

The application identified and summarized the findings of 11 published economic analyses comparing biologic therapies for moderate-to-severe plaque psoriasis (*47*–*56*). Publication dates ranged from 2013 to 2023, with the studies conducted primarily in health-care systems of high-income countries. Comparisons, time horizons and willingness-to-pay thresholds differed across the studies, but generally, adalimumab was found to be a cost-effective treatment option.

Comparative cost information for adalimumab in different markets was not available.

Availability

Adalimumab has wide global regulatory approval and market availability and is already included on many national essential medicines lists for other indications.

Biosimilar versions have been available since 2016 and potential price reductions of up to 80% have been reported compared with the innovator brand (*57*).

Among the available TNF-alfa inhibitors, infliximab biosimilars are currently the most widely disseminated option in several low- and middle-income countries and are generally associated with lower prices compared with originator products.

Other considerations

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Committee recommendations

The Expert Committee considered that the inclusion of effective and safe biological medicines for psoriasis on the Model Lists would address an important

public health need and support advocacy efforts to reduce the global burden of psoriasis, especially in low- and middle-income countries. The Committee acknowledged that a large number of biological disease-modifying medicines for psoriasis are available, and that there was a need to prioritize the most effective, tolerable and affordable options.

The Committee noted that high-quality evidence supports the superior efficacy of adalimumab and other tumour necrosis factor (TNF)-alpha inhibitors over placebo in achieving Psoriasis Area and Severity Index responses in patients with moderate-to-severe psoriasis. The Committee also noted that adalimumab and alternative TNF-alpha inhibitors were superior to the non-biological treatments (e.g. methotrexate) typically used as first-line treatment currently included on the Model Lists.

The Committee considered the safety profile of adalimumab to be well established, based on extensive clinical trial and real-world data across multiple indications. TNF-alpha inhibitors, including adalimumab, are associated with risks of serious infections and reactivation of latent tuberculosis or hepatitis B.

The Committee recalled that adalimumab and other TNF-alfa inhibitors were already included on the Model Lists for other indications and are considered to be therapeutic alternatives to each other in most clinical scenarios. The Committee considered that including multiple within-class alternatives on the Model Lists could support greater competition to lower prices. The Committee also noted the wide availability of biosimilars of these medicines, which is also an important factor in achieving lower prices.

Based on these considerations, the Expert Committee recommended the inclusion of adalimumab on the EML and EMLc for the treatment of adults and children with moderate-to-severe psoriasis. Listing is recommended for adalimumab with a square box, with certolizumab pegol, etanercept and infliximab (including quality-assured biosimilars) as therapeutic alternatives.

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Ustekinumab – addition – EML and EMLc

Ustekinumab **ATC code: L04AC05**

Proposal

Addition of ustekinumab on the complementary list of the EML and EMLc for the treatment of adults and children with severe psoriasis. Listing is requested for ustekinumab as the representative interleukin (IL)-12 and IL-23 inhibitor, with IL-23 inhibitors guselkumab, risankizumab and tildrakizumab as specified therapeutic alternatives.

Applicant

International League of Dermatological Societies

WHO technical department

Department of Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

13.4 Medicines affecting skin differentiation and proliferation

Dose form(s) & strengths(s)

EML

Injection (subcutaneous): 45 mg/0.5 mL in vial, prefilled pen and prefilled syringe; 90 mg/mL in prefilled pen and prefilled syringe

EMLc

Injection (subcutaneous): 45 mg/0.5 mL in vial and prefilled syringe; 90 mg/mL in prefilled syringe

Core/complementary

Complementary

Individual/square box listing

Square box for ustekinumab, with guselkumab, risankizumab and tildrakizumab as specified therapeutic alternatives.

Background

An application from the International League of Dermatological Societies for listing of ustekinumab for the treatment of severe psoriasis in adults was

evaluated by the Expert Committee in 2023. The Committee acknowledged the global burden of psoriasis and the public health need for effective treatments for this condition and noted that up to that time, only topical therapies were included on the Model Lists. The Committee noted that multiple randomized trials had shown ustekinumab to be more effective than placebo in the proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 and PASI 90 response. The Committee noted that biological disease-modifying therapies such as ustekinumab had an important role in the management of moderate-to-severe forms of psoriasis. The Committee noted that the network meta-analyses presented in the application demonstrated varying degrees of efficacy and toxicity among pharmacological classes and individual biological medicines in the treatment of moderate-to-severe psoriasis. The Committee considered that the optimal choice of one agent over another was not straightforward, especially when their high costs and limited availability are taken into account, which were recognized as major barriers to access in low- and middle-income countries. The Committee therefore did not recommend the inclusion of ustekinumab on the EML for the proposed indication. The Committee recommended a comprehensive review of all biological disease-modifying medicines in the treatment of moderate-to-severe forms of psoriasis be undertaken to better inform the selection of the most effective and cost-effective agents for future consideration for inclusion on the Model Lists (*1*).

In 2023, the Expert Committee recommended the addition of oral methotrexate on the complementary list of the EML and EMLc for second-line treatment of patients with psoriasis, given evidence of the favourable balance of desirable to undesirable effects (*1*).

Before 2023, only topical therapies (coal tar, corticosteroids, salicylic acid and vitamin D analogues) were included on the Model Lists for treatment of psoriasis.

Public health relevance

The public health relevance of effective treatments for psoriasis has been accepted previously by the Expert Committee.

Data for 2021 from the Global Burden of Disease study report a global prevalence of psoriasis of almost 53 million people and an annual global incidence of nearly 6 million. Psoriasis was responsible for 0.13% of global disability-adjusted life years in 2021. The prevalence was highest in the WHO Western Pacific Region and lowest in the African Region and Eastern Mediterranean Region. At the country level, the prevalence was highest in high- and middle-income countries, and lowest in low-income countries (*2*).

In children, the typical age at onset of paediatric psoriasis is between 8 and 11 years (*3*, *4*).

Patients with psoriasis have a reduced quality of life that is similar to or worse than those with other chronic diseases (5, 6). Studies have reported that patients with psoriasis also have a higher risk of death compared with individuals without the disease (7–9).

In a 2020 consensus statement from the International Psoriasis Council, patients with psoriasis are candidates for systemic therapy if they meet one or more of the following criteria: the disease affects > 10% of the body surface area, the disease involves special body areas (face, palms, soles, genitalia, scalp or nails); and topical therapy has failed for the patient topical therapy (10).

Treatment of psoriasis usually extends over the life of the patient and can involve topical therapies, systemic therapies, and phototherapy, used either individually or in combination.

Summary of evidence: benefits

Short-term efficacy studies

A 2023 Cochrane living systematic review and network meta-analysis of 179 randomized controlled trials (62 339 participants) compared benefits and harms of non-biological systemic agents, small molecules, and biologics in adults older than 18 years with moderate-to-severe plaque psoriasis. The review provided a ranking of treatments according to their benefits and harms (11). The included trials compared systemic treatments with placebo or active comparators. Patients had an average age of 44.6 years and a mean baseline Psoriasis Area and Severity Index (PASI) score of 20.4. The primary efficacy outcome was the proportion of participants who achieved clear or almost clear skin (PASI 90) at induction phase (8 to 24 weeks after randomization). Secondary efficacy outcomes included the proportion of participants who achieved PASI 75, and the proportion of participants who achieved a physician global assessment value of 0 or 1 at induction phase (11).

All interventions were superior to placebo for achieving PASI 90, with the most effective treatment being infliximab (risk ratio (RR) 49.16, 95% confidence interval (CI) 20.49 to 117.96; high-certainty evidence). In absolute terms, 934 more patients per 1000 would achieve PASI 90. For the IL-12/23 and IL-23 inhibitors proposed in the application, results versus placebo were: risankizumab RR 26.16 (95% CI 22.03 to 31.0), guselkumab RR 22.14 (95% CI 18.83 to 26.05), ustekinumab RR 17.33 (95% CI 14.76 to 20.34), and tildrakizumab RR 16.99 (95% CI 12.92 to 22.35) (all high-certainty evidence). In absolute terms, these results correspond to 497, 421, 329, and 323 more patients per 1000 achieving PASI 90, respectively (11).

Risankizumab and guselkumab were significantly more likely to result in achieving PASI 90 than adalimumab, certolizumab, deucravacitinib, etanercept and ustekinumab. PASI 90 was more likely to be achieved with the IL-17 inhibitors

bimekizumab and ixekizumab compared with secukinumab. Similarly, PASI 90 was significantly more likely to be attained by bimekizumab, ixekizumab and risankizumab compared with brodalumab and guselkumab (*11*).

In comparisons of tumour necrosis factor (TNF)-alpha inhibitors with IL 12/23 and 23 inhibitors, infliximab was significantly superior to ustekinumab (RR 2.84, 95% CI 1.17 to 6.87; moderate-certainty evidence) and tildrakizumab (RR 2.89, 95% CI 1.16 to 7.20; high-certainty evidence). Ustekinumab was significantly superior to certolizumab pegol (RR 1.43, 95% CI 1.06 to 1.91) and etanercept (1.79, 95% CI 1.60 to 2.01) (both moderate-certainty evidence). No significant difference was seen between ustekinumab and adalimumab (RR 1.07, 95% CI 0.98 to 1.18; moderate-certainty evidence). IL 23 inhibitors risankizumab and guselkumab were significantly superior to ustekinumab and all TNF-alpha inhibitors except infliximab. Surface under the cumulative ranking curve (SUCRA) rankings versus placebo for PASI 90 were: infliximab (first), risankizumab (fourth), guselkumab (eighth), ustekinumab (ninth), tildrakizumab (10th), adalimumab (11th), certolizumab (13th) and etanercept (15th). Results for the secondary efficacy outcomes (PASI 75 and physician global assessment 0/1) were comparable to the results for PASI 90 (*11*).

Long-term efficacy studies

The applicants searched the literature to identify long-term efficacy/effectiveness and safety studies on the use of adalimumab and/or ustekinumab in patients with psoriasis and identified multiple eligible studies (*12*–*34*), which were briefly summarized in Appendix 8.1 of the application. Selected studies are summarized below.

A 2021 network meta-analysis of 14 randomized controlled trials compared efficacy (measured as PASI 75/90/100) outcomes of treatments for moderate-to-severe plaque psoriasis in adults (*12*). The study included regimens for IL-12/23, IL-23, IL-17, and TNF-alpha inhibitors given for 48 to 56 weeks after randomization. No risk-of-bias assessment was conducted. The proportions of participants who achieved a PASI 90 response were: 84.9% for risankizumab; 81.3% or 79.4% for bimekizumab (depending on regimen); 78.6% for brodalumab; 77.3% for guselkumab; 72.0% for ixekizumab; 66.2% for secukinumab; 55.1% for ustekinumab; 50.8% for adalimumab; and 37.4% for etanercept. Risankizumab, bimekizumab, brodalumab, guselkumab, ixekizumab, and secukinumab significantly outperformed ustekinumab for this outcome. Ustekinumab was superior to etanercept, while there was no significant difference between ustekinumab and adalimumab.

Long-term efficacy and safety of ustekinumab, with and without dose adjustment, were evaluated in a 5-year follow-up of the PHOENIX 2 study (*24*). PHOENIX 2 was a randomized, placebo-controlled, double-blind phase III

trial of ustekinumab in adults with moderate-to-severe psoriasis. Patients were randomized to placebo, ustekinumab 45 mg, or ustekinumab 90 mg at weeks 0 and 4 and every 12 weeks thereafter. Patients receiving placebo crossed over to ustekinumab at week 12. Dosing adjustments were permitted at or beyond week 28. Efficacy and safety were evaluated through weeks 244 and 264, respectively. In patients receiving ustekinumab, 70% completed 244 weeks of treatment. PASI 75 responses were reported in 76.5% and 78.6% of patients receiving 45 mg and 90 mg doses, respectively. PASI 90 responses were reported in 50.0% and 55.5% of patients receiving 45 mg and 90 mg doses, respectively. Improved response was general observed after dose adjustment. Safety through 264 weeks was generally comparable between dose groups, and between patients with and without dose adjustments.

Observational studies

The application presented summaries of several observational studies that support longer-term efficacy and quality of life outcomes of ustekinumab (*35*–*39*). Selected studies are summarized below.

Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting was evaluated in the 2016 Psoriasis Longitudinal Assessment and Registry (PSOLAR) study (*35*). The proportions of patients achieving a physician global assessment score of 0 or 1 and mean decrease in percentage of body surface area with psoriasis were evaluated at 6 and 12 months. Data from 2076 patients were available and included in the analyses. At 6 months, the proportions of patients achieving a physician global assessment score of 0 or 1 were 57.1% for ustekinumab, 50.1% for adalimumab, 50.6% for etanercept and 36.4% for infliximab. At 12 months, the rates were 59.2% for ustekinumab, 56.5% for adalimumab, 57.6% for etanercept and 42.0% for infliximab. A greater proportion of patients receiving ustekinumab than patients receiving TNF-alpha inhibitors had a physician global assessment score that was reduced from baseline by 2 or more points at 6 and 12 months. Significant differences were seen between ustekinumab and each TNF-alpha inhibitor at 6 months, and between ustekinumab and etanercept and infliximab at 12 months. At 12 months, no significant difference was seen between ustekinumab and adalimumab (odds ratio (OR) 0.84, 95% CI 0.65 to 1.10). Mean decreases in percentage body surface area at 6 months were −14.7 for ustekinumab, −17.4 for infliximab, −11.4 for etanercept and −10.6 for adalimumab. At 6 months, the difference was only significant between ustekinumab and infliximab. At 12 months, the mean decreases in percentage body surface area were −16.3 for ustekinumab, −17.6 for infliximab, −13.8 for etanercept and −12.3 for adalimumab. At 12 months, the differences were significant between ustekinumab and infliximab and etanercept.

Comparative effectiveness at 1-year and 5-years of adalimumab, etanercept and ustekinumab in patients with psoriasis was evaluated in a 2017

study using data from the BioCAPTURE registry (*36*). A total of 513 treatment episodes involving 356 patients were included: 178, 245 and 90 episodes were related to adalimumab, etanercept and ustekinumab, respectively. The primary analysis measured differences between treatments in mean PASI score decrease over time. Over 1 year of treatment, no significant differences were seen between treatments. Over 5 years of treatment, a significant difference was seen between ustekinumab and etanercept, but not between other treatments. The proportion of patients with PASI 75 was investigated in a secondary analysis. Results showed that at 1 year, patients treated with adalimumab and ustekinumab had a higher chance of achieving PASI 75 than patients given etanercept.

A 2017 prospective cohort study using data the from the British Association of Dermatologists Biologic Interventions Register compared changes in health-related quality of life in patients with psoriasis receiving adalimumab, etanercept and ustekinumab (*37*). A total of 2152 patients (1239, 517 and 396 receiving adalimumab, etanercept and ustekinumab, respectively) were included. Median changes from baseline to 12 months in the Dermatology Life Quality Index were −11 (interquartile range (IQR) −19 to −6) for etanercept, −14 (IQR −19 to −8) for adalimumab and −14 (IQR −20 to −7) for ustekinumab. The proportions of patients achieving a Dermatology Life Quality Index score of 0/1 at 12 months were 33.1%, 54.6% and 50.2% for etanercept, adalimumab and ustekinumab, respectively. The proportions of patients achieving an improvement of ≥ 4 points from baseline in Dermatology Life Quality Index scores at 12 months were 84.6%, 86.5% and 85.9% for the three treatments, respectively. Changes from baseline to 12 months in the EuroQoL-5D utility scores were 0.12 (IQR 0.00 to 0.28) for etanercept, 0.11 (IQR 0.00 to 0.27) for adalimumab and 0.07 (IQR 0.00 to 0.28) for ustekinumab.

Paediatric patients

A 2020 retrospective cohort study assessed 6-month reduction in psoriasis severity associated with methotrexate and biologic medicines in the treatment of paediatric patients < 18 years with moderate-to-severe psoriasis (*16*). A total of 234 participants were included, of whom 163 received only methotrexate, 47 received only biologics and 24 received sequential treatment with methotrexate and biologics or vice versa. Of the participants who received biologics, 52 (73.2%) received etanercept, 14 (19.7%) received adalimumab, four (5.6%) received ustekinumab, and one (1.4%) received infliximab. The results were not stratified by the different biologic agents. Among participants evaluated at 6-months follow-up, PASI 75 was achieved in 40.0% (12/30) treated with methotrexate compared with 71.4% (20/28) treated with biologics (OR 4.56, 95% CI 2.02 to 10.27; $P < 0.001$). Physician global assessment scores of 0 or 1 were reported for 35.6% (41/115) and 48.6% (18/37) participants treated with methotrexate and biologics, respectively (OR 2.00, 95% CI 0.98 to 4.00; $P = 0.06$).

Summary of evidence: harms

In the 2023 Cochrane living systematic review and network meta-analysis, the primary safety outcome was the proportion of participants with serious adverse events (death, life-threatening events, initial or prolonged hospitalizations, and adverse events requiring intervention to prevent permanent impairment or damage) at the induction phase (*11*). No significant differences were seen between active interventions versus placebo in the risk of serious adverse events, although methotrexate, ciclosporin, infliximab, certolizumab, alefacept, apremilast, and fumaric acid esters had a lower probability of serious adverse events compared with ustekinumab. Considering TNF-alpha inhibitors IL-12-23 and IL-23 inhibitors, SUCRA rankings versus placebo for serious adverse events were: risankizumab (third), certolizumab (fifth) and etanercept (sixth), tildrakizumab (eighth), guselkumab (11th), ustekinumab (13th), adalimumab (14th) and infliximab (19th).

In the 2001 network meta-analysis, the reported safety outcomes were the proportion of patients who experienced any adverse event, any serious adverse event or adverse events leading to treatment discontinuation (*12*). Eight trials for seven treatments were included. Rates of any adverse event were 67.5% for risankizumab, 72.2% for guselkumab, 72.9% for adalimumab, 76.6% for secukinumab, 76.9% for ustekinumab, 80.9% for ixekizumab and 82.3% for bimekizumab. Significantly lower rates of any adverse event were observed for risankizumab compared with secukinumab, ustekinumab and bimekizumab, and for guselkumab compared with bimekizumab. No other statistically significant differences were identified. Rates of serious adverse events were 4.4% for risankizumab, 5.4% for adalimumab, 5.7% for ustekinumab, 5.9% for guselkumab, 6.9% for secukinumab, 7.2% for bimekizumab and 10.5% for ixekizumab. Rates of adverse events leading to treatment discontinuation were 0.9% for risankizumab, 2.2% for ustekinumab, 2.5% for guselkumab, 3.2% for secukinumab, 3.4% for adalimumab, 4.1% for bimekizumab and 4.3% for ixekizumab. No significant differences were seen between treatments for serious adverse events or adverse events leading to treatment discontinuation.

Findings from registry studies suggest that ustekinumab was not associated with an increased risk of serious infections compared with methotrexate or TNF-alpha inhibitors (*18*, *22*, *33*). Ustekinumab does not appear to be associated with an increased risk of active tuberculosis (*30*), or increased long-term risk of malignancies (*20*, *28*).

Paediatric patients

A 2017 retrospective cohort study evaluated the safety of systemic therapies for treatment of moderate-to-severe psoriasis in paediatric patients (*15*). A total of 390 children (mean age at diagnosis 8.4 years) were included, of whom 270

(69.2%) received methotrexate, 80 (20.5%) received etanercept, 19 (4.9%) received adalimumab, five (1.3%) received ustekinumab, two (0.5%) received infliximab and 106 (27.2%) received other non-biologic therapy. Of the participants treated with ustekinumab, ≥ 1 treatment-related adverse event was reported in 3/5 (60.0%). Adverse events reported were infections, fatigue and diarrhoea. One participant treated with ustekinumab experienced ≥ 1 adverse event leading to treatment discontinuation.

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of psoriasis are not currently available.

Costs/cost–effectiveness

The application presented information on list prices in local currency for ustekinumab products from mainly upper middle- and high-income countries worldwide. Prices ranged from about 540 United States dollars (US$) in the Republic of Korea to almost US$ 14 000 in the United States of America for the 45 mg strength injections, and from US$ 570 in Poland to almost US$ 28 000 in the United States for the 90 mg strength injections. Where generic forms were available, price reductions were often reported.

A 2023 study modelled the cost per PASI 100 responder of biologic medicines for moderate-to-severe plaque psoriasis in France and Germany (*40*). The model included IL-17 inhibitors (bimekizumab, brodalumab, ixekizumab and secukinumab), IL-23 inhibitors (guselkumab risankizumab and tildrakizumab), TNF-alpha inhibitors (adalimumab, etanercept, certolizumab and infliximab) and ustekinumab. The cost per PASI 100 responder for ustekinumab after 1 year of treatment was 35 666 euros (€) and €72 078 in France and Germany, respectively. In comparison, the costs per PASI 100 responder for adalimumab were €23 418 and €38 264. Brodalumab had the lowest costs per PAS 100 at €20 220 and €26 807.

The application identified and summarized the findings of 15 published pharmacoeconomic studies comparing biologic therapies for moderate-to-severe plaque psoriasis (*40*–*54*). Publication dates ranged from 2011 to 2023, with the studies conducted primarily in health-care systems of high-income countries. Comparisons, time horizons and willingness-to-pay thresholds differed across the studies.

In a 2014 cost–effectiveness study comparing ustekinumab and TNF-alpha inhibitors conducted from the Italian health-care system perspective, ustekinumab had the lowest cost per responder compared with adalimumab, etanercept and infliximab. Ustekinumab (45 mg) was cost-effective versus

adalimumab and etanercept, with incremental cost-effectiveness ratios of €10 632 per quality-adjusted life year (QALY) and €28 602 per QALY, respectively. Ustekinumab was cost-saving versus infliximab (*48*). The other studies presented in the application generally supported the cost–effectiveness of ustekinumab in various settings, circumstances and versus various comparators.

Availability

The application reported that ustekinumab had regulatory approval for use in plaque psoriasis in Australia, Canada, European Union, Japan, Saudi Arabia, Singapore, Switzerland, United Kingdom of Great Britain and Northern Ireland and United States. Market availability varies considerably between countries and regions.

Biosimilar versions have been available since 2023 in some settings, with price reductions compared to the innovator brand reported.

Other considerations

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Committee recommendations

The Expert Committee considered that the inclusion of effective and safe biological medicines for psoriasis on the Model Lists would address an important public health need and support advocacy efforts to reduce the global burden of psoriasis, especially in low- and middle-income countries. The Committee acknowledged that a large number of biological disease-modifying medicines for psoriasis are available and that there was a need to prioritize the most effective, tolerable and affordable options.

The Committee noted that high-quality evidence supports the superior efficacy of ustekinumab and other interleukin 12/23 and IL-23 inhibitors over placebo in achieving Psoriasis Area and Severity Index responses in patients with moderate-to-severe psoriasis. The Committee also noted moderate-certainty evidence that ustekinumab had superior or similar effectiveness to tumour necrosis factor (TNF)-alpha inhibitors, with the exception of infliximab, which was significantly superior to ustekinumab. The Committee acknowledged the data supporting superior or similar effectiveness of other IL-23 inhibitors, guselkumab, risankizumab and tildrakizumab, compared with ustekinumab.

The Committee noted that the safety and acceptability of ustekinumab were similar to that of adalimumab. Additionally, Committee noted that ustekinumab was preferred to adalimumab in patients with heart disease and in settings where tuberculosis was endemic as it is associated with a lower risk of tuberculosis reactivation.

The Committee considered that ustekinumab may offer advantages over adalimumab in the administration schedules of the two medicines. Ustekinumab

is given every 12 weeks, while adalimumab is given every 2 weeks. The Committee agreed that less frequent injections are more convenient, with reduced disruption to daily life for patients, and reduced burden and costs for health systems.

The Committee acknowledged the current high price of ustekinumab, but that it had been found to be cost-effective in some high-income settings. The Committee also noted that biosimilars of ustekinumab had recently become available, which will be an important factor in achieving lower prices. However, ustekinumab biosimilars are less commonly available than some anti-TNF alfa agents (e.g. infliximab, adalimumab). The Committee recognized that the implementation of recommendations concerning ustekinumab will progress at different speeds, depending on the capacity of individual healthcare systems. In low-income countries, anti-TNF alfa agents are most likely to represent the class of medicines with the best benecit-cost ratio after methotrexate.

Based on these considerations, the Expert Committee recommended the inclusion of ustekinumab (including quality-assured biosimilars) on the complementary list of the EML and EMLc for the treatment of adults and children with moderate-to-severe psoriasis. However, the Committee did not recommend listing it with a square box to include guselkumab, risankizumab and tildrakizumab as therapeutic alternatives. The Committee considered that these medicines had less supportive evidence than ustekinumab, biosimilars are not yet available and there was no information on costs, which were assumed to be higher than for ustekinumab.

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13.6 Emollients

Urea- and glycerol-based topical moisturizers – addition – EML and EMLc

Glycerol	**ATC code: D02AX**
Glycerol + liquid paraffin + white soft paraffin	**ATC code: D02AC**
Urea (INN carbamide)	**ATC code: D02AE01**

Proposal

Addition of glycerol- and urea-based topical moisturizers on the core list of the EML and EMLc for the treatment of atopic dermatitis in adults and children.

Applicant

International Society of Atopic Dermatitis; WHO Department of Control of Neglected Tropical Diseases

WHO technical department

Department of Control of Neglected Tropical Diseases

EML/EMLc

EML and EMLc

Section

13.6 Emollients

Dose form(s) & strengths(s)

Glycerol

Cream: 15%–20%

Glycerol + liquid paraffin + white soft paraffin

Cream: 15% + 2% + 8%

Urea

Cream: 5%

The applicants used regulatory authority databases of medicinal products to identify emollients and protectives for the treatment of atopic dermatitis. Authorized products identified included those above proposed for listing, as well as products containing different strengths of glycerol and/or urea in combination with other components, as well as propylene glycol-based products. The other products were not proposed for addition to the Model Lists because of limited evidence of their clinical efficacy in the treatment of dryness in atopic dermatitis and/or limited evidence of a positive effect on skin barrier function (e.g. lowering of transepidermal water loss).

Core/complementary

Core

Individual/square box listing

Individual

Background

Urea (10% cream and ointment) was added to the EML in 1995 and to the EMLc in 2007 as a keratolytic agent (*1*, *2*). A 5% strength was added in 2011 (*3*).

Glycerol-based topical moisturizers have not previously been considered for inclusion on the Model Lists as topical moisturizers.

Public health relevance

According to the Global Burden of Disease Study, 171 million individuals were affected with atopic dermatitis in 2019, with age-standardized prevalence and incidence rates that were relatively stable from 1990 to 2019. Prevalence rates show some regional trends, with the highest prevalence reported in the Asian Pacific and Central Asian regions, and the lowest prevalence reported in the African region (*4*).

Individuals with atopic dermatitis have a reduced quality of life (*5*–*8*), where the stigma associated with its visibility and itch affects sufferers (*9*, *10*). Sleeplessness may lead to poor work functioning and decreased skills (*11*), school absenteeism and lower learning outcomes in children (*12*). Untreated atopic dermatitis can be associated with secondary skin and systemic infections (*13*). Furthermore, eczema is a time-consuming and costly disease to treat (*6*), similar to the costs of other chronic diseases (*14*).

Summary of evidence: benefits

The application identified seven systematic reviews published between 2015 and 2023 that evaluated the effectiveness and safety of topical moisturizers (*15*–*21*). Findings from a 2017 Cochrane systematic review of 77 randomized controlled trials (6603 participants) that evaluated the effects of moisturizers for the treatment of eczema are summarized below (*17*). The other systematic reviews identified in the application were either published before the Cochrane review or did not report outcomes specifically for glycerol- and urea-based moisturizers. All reviews provided evidence of the beneficial effects of moisturizers generally in the treatment of atopic dermatitis.

For the comparison of moisturizers versus no moisturizer, there was low-certainty evidence that moisturizer use was effective in reducing disease severity compared with no moisturizers as assessed using Scoring Atopic Dermatitis (SCORAD) scores (mean difference (MD) −2.42, 95% confidence interval (CI)

−4.55 to −0.28; three randomized controlled trials, 276 participants). However, the minimal important difference in SCORAD score (8.7) was not met.

For the comparison of all moisturizers versus vehicle, placebo or no moisturizer, there was high-certainty evidence that moisturizers were associated with reduced investigator-assessed disease severity from baseline (standardized MD (SMD) −1.04, 95% CI −1.57 to −0.51; 12 randomized controlled trials, 1281 participants), and moderate-certainty evidence of a reduced risk of eczema flare-ups (risk ratio (RR) 0.33, 95% CI 0.17 to 0.62; six randomized controlled trials, 607 participants). There was low-certainty evidence that moisturizers were associated with lower participant-assessed disease severity (RR 2.46, 95% CI 1.16 to 5.23; five randomized controlled trials, 572 participants), and that moisturizer use was associated with patient-assessed benefit in terms of reduced itch (SMD −1.10, 95% CI −1.83 to −0.38; seven randomized controlled trials, 749 participants). There was low-certainty evidence of no significant differences between treatment groups for patient satisfaction (RR 1.35, 95% CI 0.77 to 2.26; three randomized controlled trials, 296 participants).

For the comparison of urea-containing moisturizer versus vehicle, placebo or no moisturizer, there was moderate-certainty evidence of improvement in disease severity as assessed by investigators favouring urea-containing moisturizers (RR 1.40, 95% CI 1.14 to 1.71; one randomized controlled trial, 129 participants). There was low-certainty evidence of improvement in disease severity as assessed by participants favouring urea-containing moisturizers (RR 1.28, 95% CI 1.06 to 1.53; one randomized controlled trial, 129 participants). There was also low-certainty evidence that fewer participants using urea-containing moisturizers experienced a disease flare-up (RR 0.47, 95% CI 0.24 to 0.92; one randomized controlled trial, 44 participants).

For the comparison of glycerol-containing moisturizer versus vehicle or placebo, there was high-certainty evidence of improvement in disease severity as assessed by investigators using SCORAD favouring glycerol-containing moisturizer (MD −2.2, 95% CI −3.4 to −0.96; one randomized controlled trial, 249 participants), however, the minimal important difference was not met. There was moderate-certainty evidence of improvement in disease severity as assessed by participants favouring glycerol-containing moisturizers (RR 1.22, 95% CI 1.01 to 1.48; one randomized controlled trial, 134 participants).

For the comparison of topical active treatment (corticosteroids or calcineurin inhibitors) plus moisturizer versus moisturizer alone, there was moderate-certainty evidence of improvement in disease severity as assessed by investigators using SCORAD favouring combination treatment (MD −0.87, 95% CI −1.17 to −0.57; three randomized controlled trials, 192 participants) and low-certainty evidence of fewer flare-up (RR 0.43, 95%CI 0.20 to 0.93; one randomized controlled trial, 105 participants).

Summary of evidence: harms

In the 2017 Cochrane systematic review, for the comparison of all moisturizers versus vehicle, placebo or no moisturizer, there was moderate-certainty evidence of no significant difference between treatment groups in the number of participants experiencing adverse events (RR 1.03, 95% CI 0.82 to 1.30; 10 randomized controlled trials, 1275 participants). For the comparison of urea-containing moisturizers versus vehicle, placebo or no moisturizer, there was moderate-certainty evidence of an increased risk of adverse events in participants using urea-containing moisturizer (RR 1.65, 95% CI 1.16 to 2.34; one randomized controlled trial, 129 participants). For the comparison of glycerol-containing moisturizers versus vehicle or placebo, there was moderate-certainty evidence of no significant difference between treatment groups in the number of participants experiencing adverse events (RR 0.90, 95% CI 0.68 to 1.19; two randomized controlled trials, 385 participants) (*17*).

Moisturizers are generally safe with a favourable safety profile. The most common adverse effects are mild and transient skin reactions, such as stinging, itching and redness. These reactions are more likely to occur in patients with impaired skin barrier function, such as those with atopic dermatitis. Urea-containing creams may cause more frequent adverse events compared with other moisturizers, but these are typically mild and temporary.

Additional evidence

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WHO guidelines

WHO guidelines for the treatment of atopic dermatitis are not currently available.

Various regional treatment recommendations and national and international guidelines include recommendations for the use of moisturizers as first-line treatment for atopic dermatitis in adults and children (*8*,*21*–*23*).

Costs/cost–effectiveness

No cost–effectiveness evidence was presented in the application.

The application estimated formulation, packaging and production costs for the proposed moisturizers of around 25–50 euros (€) per year for adults and €18–36 per year for children, assuming use of about 70–140 g/week in adults and of 50–100 g/week in children.

The application reported that in many resource-limited settings, moisturizing creams are available as imported, over-the-counter cosmetic products and are subject to high taxation, making them unaffordable for many patients.

Availability

The application reports that the proposed moisturizers are authorized as medicinal products in several European countries, and pharmacopeial standards for glycerol and urea are available.

Topical urea formulations are already included on national essential medicines lists of more than 30 countries. One commercial brand of glycerol 15% cream was reported in the application to be available in 32 countries.

Other considerations

–

Committee recommendations

The Expert Committee acknowledged the substantial public health burden of atopic dermatitis, its particularly high prevalence in children, and its effects on skin integrity and quality of life. The Committee also noted the challenges faced in many resource-constrained settings to provide affordable access to therapeutic moisturizing agents for the treatment of atopic dermatitis and prevention of symptom worsening and disease flares. The Committee recognized that regular use of therapeutic moisturizers helps maintain skin barrier function, reduces dryness and irritation, and can prevent exacerbations of atopic dermatitis, thereby improving overall disease control.

The Committee noted the availability of many different moisturizing products, variably regulated as therapeutics or cosmetics, and recognized the need to prioritize the most effective, best tolerated and affordable therapeutic options. The Committee considered that the rationale used by the applicants to prioritize the proposed glycerol- and urea-based moisturizers was sufficiently robust and evidence-based.

The Committee considered evidence from multiple systematic reviews that support the efficacy and safety of topical moisturizers, generally, in the treatment of atopic dermatitis. In consideration of glycerol- and urea-based moisturizers, some evidence suggests that these were associated with improvements in disease severity and prevention of flare-ups. However, the Committee noted that the quality of evidence varied and that the magnitude of clinical benefit was modest in some analyses. The safety profile of glycerol- and urea-based moisturizers was considered favourable. Adverse effects were generally mild and transient. Urea-containing moisturizers were associated with a slightly higher frequency of local reactions compared with glycerol-containing moisturizers, but both were safe for long-term use.

The Committee noted that while cost–effectiveness data were not provided, the estimated annual treatment costs were considered a reasonable indicator of feasibility of implementation in national programmes and sufficient to support

decision making. However, affordability remains a challenge in many resource-constrained settings, particularly where moisturizers are imported and taxed as cosmetics. The Committee emphasized the importance of local production and regulatory classification as medicinal products to improve access and affordability.

The Committee noted and appreciated the contributions submitted during the public consultation process for the application, indicating support for the proposal to include glycerol- and urea-based moisturizers on the Model Lists.

The Expert Committee therefore recommended the inclusion of glycerol- and urea-based moisturizing creams on the EML and EMLc for the treatment of atopic dermatitis based on evidence of benefit, acceptable safety and public health need. Recommended formulations are creams containing 15% to 20% glycerol and creams containing 5% urea and with regulatory approval as emollients. The Committee emphasized the importance of ensuring access to affordable, quality-assured therapeutic moisturizers as part of comprehensive management of atopic dermatitis, particularly in resource-constrained settings. Any future applications for inclusion of new therapeutic moisturizers should consider glycerol- and urea-based formulations as the standard comparator, given their established efficacy, safety and affordability profile.

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13.7 Sunscreens, broad-spectrum

Sunscreen – addition – EML and EMLc

Sunscreen, broad-spectrum	ATC code: D02BA

Proposal

Addition of broad-spectrum sunscreen with sun-protection factor (SPF) 50+ to the core list of the EML and EMLc for the prevention of skin cancer in persons with albinism.

Applicant

Muluka-Anne Miti-Drummond, UN Independent Expert on the Enjoyment of Rights by Persons with Albinism

WHO technical department

The cancer team within the Department of Noncommunicable Diseases Rehabilitation and Disability reviewed the application and supported the inclusion of topical broad-spectrum sunscreen on the Model Lists to reduce the risk of skin cancer in the target population.

EML/EMLc

EML and EMLc

Section

13.7 Sunscreens

Dose form(s) & strengths(s)

Topical (balm, cream, lotion, stick, gel, oil, paste, spray): sun protection factor (SPF) 50+

Core/complementary

Core

Individual/square box listing

Individual

Background

Sunscreen products are not currently included on the Model Lists. Previous listings of p-aminobenzoic acid, benzophenones, zinc oxide and broad-spectrum topical sunscreen (containing 3% octyl methoxycinnamate, 2% titanium dioxide

and 2% butyl methoxydibenzoylmethane) were removed from the EML in 2005. The Expert Committee noted that while sunscreens were effective in preventing squamous cell skin cancer in susceptible individuals, they were not normally provided by public facilities (*1*).

An application for the re-introduction of topical sunscreen products on the Model Lists for the prevention of skin cancer in people with albinism was considered by the Expert Committee in 2023 (*2*). The Committee acknowledged that people with albinism had a significantly higher risk of skin cancer due to the harmful effects of ultraviolet (UV) radiation and were a population for whom the use of broad-spectrum sunscreen was an important preventive intervention. The Committee also acknowledged the public health relevance and effectiveness of sunscreen in preventing skin cancer in both the general population and in people with albinism. The Committee noted that many different sunscreen products were available on global markets, containing a wide variety of organic agents (which absorb UV radiation) and/or inorganic agents (which reflect of scatter UV radiation). Sunscreen products also vary widely in their sun protection factor rating and are subject to different regulatory standards (e.g. regulated as therapeutics or as cosmetic products) in different jurisdictions. The Committee considered that before being able to recommend sunscreen products for inclusion on the Model Lists, it would be necessary to define relevant standards and specifications for therapeutic (as distinct from cosmetic) sunscreen products protecting against both UVA and UVB radiation. This would include evidence-based details of specific active ingredients and their concentration, and the range of sun protection factor rating. The Expert Committee therefore did not recommend listing at that time but requested WHO undertake the necessary work to inform a resubmission for consideration in 2025.

Public health relevance

Albinism is a genetic condition characterized by decreased or absent pigmentation (melanin) in the hair, skin and/or eyes. Melanin is crucial for protecting the skin from sun damage. Individuals with albinism are highly vulnerable to UV radiation, which significantly increases their risk of skin cancer and other UV-induced skin disorders. The lack of melanin in people with albinism leads to a higher susceptibility to acute and chronic actinic damage, including solar elastosis, actinic keratosis and skin cancers (*3*–*5*).

Albinism occurs worldwide, with varying prevalence rates. In European countries, the prevalence ranges from 1:14 000 to 1:17 000, while in African countries, prevalence ranges from 1:1500 to 1:15 000 (*6*, *7*).

Studies have shown that people with albinism in some African countries are 1000 times more likely to develop squamous cell carcinoma than the general population (*8*, *9*). Additionally, individuals with albinism predominantly develop

skin cancers by the time they are 20 years old and often do not live beyond the age of 30 years (*8*, *10*, *11*). Further studies have shown that, without sunscreen, children with albinism can develop chronic skin damage from as young as 12 months (*12*). The development of skin cancer in persons with albinism is correlated to their occupation, with occupations that chronically expose skin to sunlight associated with higher occurrence of skin cancers (*13*).

Summary of evidence: benefits

No new evidence for benefits was presented in the current application compared with the previous application. The following summary is reproduced from the technical report of the 2023 Expert Committee meeting (*2*).

The topical application of broad-spectrum sunscreens is recommended as a safe adjunct measure in protecting human skin from UV radiation when other protection measures (e.g. clothing or sun avoidance) cannot be used or are insufficient. In the context of persons with albinism, sunscreen use is considered part of healthy sun protection practices (*14*).

Research has shown the benefits of using sunscreen in reducing the incidence of skin cancer (*15*).

A randomized trial of 1621 adults in Australia evaluated daily sunscreen application (SPF 15+) versus no daily sunscreen for the prevention of squamous cell and basal cell carcinomas (*16*). After 4.5 years of follow-up, no significant differences were reported in the incidence of first new skin cancers between the daily sunscreen and no daily sunscreen groups: basal cell carcinoma 2588 versus 2509 per 100 000 (rate ratio (RR) 1.03, 95% confidence interval (CI) 0.73 to −1.46) and squamous cell carcinoma 876 versus 996 per 100 000 (RR 0.88, 95% CI 0.50 to 1.56). In terms of the number of tumours, no effect was observed on the incidence of basal cell carcinoma by sunscreen use. However, the incidence of squamous cell carcinoma was significantly lower in the daily sunscreen group than the no daily sunscreen group (1115 versus 1832 per 100 000; RR 0.61, 95% CI 0.46 to 0.81). After a further 8 years of follow-up, a non-significant decrease in rates of basal-cell carcinoma tumour was found in the daily sunscreen group compared with the no sunscreen group. For rates of squamous-cell carcinoma tumour, a significant decrease was observed in the daily sunscreen group compared with the no sunscreen group (RR 0.62, 95% CI 0.38 to 0.99) (*17*).

A 2022 study using data from the United States National Health and Nutritional Examination Survey (2015–2016) evaluated the association of sunscreen use, sun avoidance and wearing of protective clothing with skin cancer prevalence (*18*). Sunscreen use was the only intervention that showed a statistically significant reduction in skin cancer prevalence (odds ratio 3.75, 95% CI 1.78 to 8.89).

A retrospective study compared the effects of sun exposure on the occurrence of skin cancers in 22 participants with albinism and 30 without

albinism (*19*). The average ages of participants with and without albinism with skin cancers were 34.6 years and 65.1 years, respectively. Of the participants with skin cancers, about 43% those with albinism and 80% of those without albinism reported prolonged sun exposure. Among participants with albinism who had used sunscreen since childhood, 2/19 (10.5%) developed skin cancer, while of participants with albinism who did not use sunscreen, 20/27 (74.1%) developed skin cancer.

A 2021 expert panel review investigated the effect of solar wavelength according to skin phototype and dermatoses, and proposed the need for tailoring recommendations for sunscreen type accordingly, as well as taking into consideration geographical latitude and altitude (*20*). For example, protection against UVB radiation is especially important for light skin as there is a high risk of sunburn, DNA damage and skin cancers. Darker skin may be naturally better protected against UVB but is more prone to hyperpigmentation induced by visible light and UVA radiation. For the prevention of skin cancers, the expert panel recommended daily use of sunscreen with high SPF (50+) and good UVA protection factor, and an SPF to UVA protection factor ratio between 1 and 3.

Summary of evidence: harms

No new evidence for harms was presented in the current application compared with the previous application. The following summary is reproduced from the technical report of the 2023 Expert Committee meeting (*2*).

Concerns about the toxicity of UV filters and reduced vitamin D synthesis related to the use of sunscreen have been raised. The management of sunscreens must therefore balance their essential protective effect against the potential toxicity of the UV filters for humans and the environment.

Photoallergic reactions are the most common adverse effect of topical sunscreens. This effect is particularly associated with the benzophenone class of organic UV filters. Contact dermatitis and photoallergy have also been reported with ethylhexyl methoxycinnamate and octocrylene. Allergenic effects are rare with mineral UV filters (e.g. titanium dioxide), but concerns have been raised about systemic absorption of micronized particles (*21*). A review of titanium dioxide in nanoparticle form found no evidence of carcinogenicity, mutagenicity or toxicity following dermal exposure. However, there are restrictions in Europe on the use of nanoparticle titanium dioxide formulations that can lead to lung exposure through inhalation (e.g. spray and powder products) (*22*).

A quasi-experimental study conducted during winter in Brazil evaluated vitamin D synthesis with suberythemal sun exposure in 95 adults (*23*). Participants were randomized to one of three groups: use of SPF 30 sunscreen on the face, neck and chest ($n = 64$), no sunscreen ($n = 10$) or no sun exposure ($n = 21$). No difference was found between the sunscreen and no sunscreen groups for change

in vitamin D level from baseline to 24 hours after sun exposure (5.4 ng/mg, 95% CI 4.4 to 6.5 ng/mg versus 4.1 ng/mg, 95% CI 2.5 to 6.0 ng/mg; $P < 0.01$).

A literature review of sunscreen photoprotection and vitamin D status identified nine controlled studies on the effect of daily/recreational sunscreen use on vitamin D synthesis (*24*). Seven of the studies showed no change in serum vitamin D with sunscreen use. Two studies found a reduction in vitamin D levels with sunscreen use. However, the studies did not consider important factors that may have influenced the outcome, such as personal UV exposure, thickness of sunscreen application and exposed body surface area. The authors of the review concluded that broad-spectrum sunscreen use was unlikely to compromise vitamin D status in healthy populations.

Sunscreens may cause environmental harm (*15*). In this regard, some regulatory agencies have updated the indications, doses, labelling and testing of over-the-counter sunscreen agents (*25*).

Additional evidence

The application presented a summary of active sunscreen ingredients with approved concentration ranges as listed by selected regulatory agencies (United States Food and Drug Administration, Health Canada, Australian Therapeutic Goods Administration, Medsafe New Zealand, and EU Cosmetic Regulation No 1223/2009), Table 10.

Table 10
Characteristics of active sunscreen ingredients

Active ingredient	Concentration	Molecular class	Wavelengths absorbed/filtered
Amiloxate	Up to 10%	Organic	UVB
Avobenzone	Up to 3%	Organic	UVA (primarily UVA I)
Bemotrizinol	Up to 10%	Organic	UVA and UVB
Benzylidene camphor sulfonic acid	Up to 6%	Organic	UVA and UVB
Bisdisulizole disodium	Up to 10%	Organic	UVA
Bisoctrizole	Up to 10%	Organic	UVA and UVB
Cinoxate	Up to 3%	Organic	UVB
Diethylamino hydroxybenzoyl hexyl benzoate	Up to 10%	Organic	UVA

Table 10 *continued*

Active ingredient	Concentration	Molecular class	Wavelengths absorbed/filtered
Dimethicodiethylbenzalmalonate	Up to 10%	Organic	UVB
Dioxybenzone	Up to 3%	Organic	UVA and UVB
Drometrizole trisoloxane	Up to 15%	Organic	UVA and UVB
Ecamsule	Up to 10%	Organic	UVA (primarily UVA II)
Ensulizole	Up to 4%	Organic	UVB (some UVA)
Enzacamene	Up to 4%	Organic	UVB
Ethoxylated ethyl 4-aminobenzoic acid	Up to 10%	Organic	UVB
Ethylhexyl triazone	Up to 5%	Organic	UVB
Iscotrizinol	Up to 10%	Organic	UVA
Octinoxate	Up to 7.5%	Organic	UVB
Octisalate	Up to 5%	Organic	UVB
Padimate-O	Up to 8%	Organic	UVB
Phenylene bis-diphenyltriazine	Up to 5%	Organic	UVA and UVB
Polyacrylamidomethyl benzylidene camphor	Up to 6%	Organic	UVB
Sulisobenzone	Up to 5%	Organic	UVA and UVB
Terephthalylidene dicamphor sulfonic acid	Up to 10%	Organic	UVA
Titanium dioxide	Up to 25%	Mineral/ inorganic	UVB (some UVA)
Tris-biphenyl triazine	Up to 10%	Organic	UVA and UVB
Zinc oxide	Up to 25%	Mineral/ inorganic	UVA (I and II) and UVB

UV: ultraviolet.

The International Organization for Standardization (ISO) provides standards for sun protection test methods and the determination of sun protection factor and UVA-protection factor of sunscreens.

The application stated that sunscreen is a complex product in which the final formulation is crucial. However, evidence is lacking to support one particular formulation over any others. Therapeutic broad-spectrum sunscreens should be formulated and tested according to the relevant ISO standards, have an SPF of 50+ and filter both UVA and UVB radiation. The UVA to UVB ratio is recommended to be 1:3.

The International League of Dermatological Societies advocates for the use of broad-spectrum sunscreen with a minimum SPF of 30 in populations at risk of skin cancers, including individuals with albinism. The guidelines stress the importance of reapplication after swimming or sweating to maintain effective protection (*26*).

WHO guidelines

WHO guidelines for the use of sunscreen are not currently available.

WHO recommends the use of broad-spectrum sunscreen on skin areas that cannot be covered by clothes, as one of a series of recommended measures to protect against excessive UV exposure (*27*).

Various national and international dermatology societies recommend regular application of a water-resistant, broad-spectrum sunscreen providing UVA and UVB protection and with an SPF of at least 30 (sometimes 50), in addition to other sun protection measures.

Costs/cost–effectiveness

No new costs or cost–effectiveness data were presented in the current application compared with the previous application. The following summary is reproduced from the technical report of the 2023 Expert Committee meeting (*2*).

Skin cancer is a significant cost and population burden for many countries and expenditure will grow as incidence increases. Public investment in skin cancer prevention and early detection programmes suggest health and economic benefits (*28*).

While many people with albinism are aware of the need to protect themselves from the harmful effects of UV radiation, studies have shown that they are prevented from doing so due to the cost of sunscreen, as well as the cost of travel and travel distance to enable them to obtain sunscreen (*29*).

Studies have concluded that systematic sunscreen use at a population level will prevent substantial numbers of new skin lesions and reduce the costs of treatment and loss of life (*30*–*32*).

An Australian study evaluated daily versus discretionary sunscreen use and considered the use of health-care resources, costs and health outcomes from the prevention of basal-cell carcinoma and squamous cell carcinoma (*32*). From a societal perspective, over 5 years, the net costs for daily versus discretionary sunscreen use

were 329 149 United States dollars (US$) and US$ 222 700, respectively. The cost for the daily sunscreen group was offset in part by reduced costs for medical treatment as a result of skin cancers and actinic keratoses avoided. From the Australian government perspective (as funder of medical care for treatment of skin cancers), daily sunscreen use was cost-saving compared with discretionary sunscreen use.

Availability

Sunscreens are widely available as personal care products or over-the-counter medicines in most middle- and high-income countries. Availability and affordability in lower-income countries are more limited. The application highlighted that availability and affordability will need to be supported by government programmes in lower-income settings.

Definitions and labelling standards are set by national regulatory agencies.

Other considerations

From the human rights perspective, the United Nations Human Rights Committee has stated that "the obligation of States parties to respect and ensure the right to life extends to reasonably foreseeable threats and life-threatening situations that can result in loss of life" (*33*).

Access to sunscreen by people with albinism is a right under Article 12 of the International Covenant on Economic, Social and Cultural Rights (*34*), which enshrines the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, as well as Article 25 of the Convention of the Rights of Persons with Disabilities (*35*), particularly Article 25(b) which requires states to "provide those health services needed by persons with disabilities specifically because of their disabilities".

Committee recommendations

The Expert Committee recognized the public health relevance of broad-spectrum sunscreen for the prevention of skin cancer in people with albinism, a population at significantly elevated risk of UV-induced skin damage and skin cancers. The Committee acknowledged that sunscreen is often the only feasible barrier to UV exposure for exposed skin, particularly where clothing or shade is insufficient. The Committee noted that no treatments are currently listed on the EML or EMLc for the prevention of UV-induced skin damage or skin cancer in people with albinism. While sunscreens were previously included on the EML, they were removed in 2005 due to challenges that provision was not a public sector remit, despite their demonstrated efficacy. The Committee acknowledged that the previous decision to remove sunscreens from the Model Lists may have negatively impacted people with albinism, as provision for this high-risk group should be recognized as a public sector responsibility.

The Committee accepted the effectiveness and safety of broad-spectrum sunscreens in reducing the risk of skin cancer in all populations. The Committee considered that the protective role of sunscreen in preventing skin cancer was especially relevant in high-risk groups, such as people with albinism. The Committee also highlighted that sunscreen use alone should not be the only sun protection strategy used and stressed the importance of other measures (where possible) such as sun avoidance, shade seeking and sun-protective clothing.

The Committee considered that the application addressed the concerns of the 2023 Expert Committee in presenting information on international standards for SPF determination, as well as recommended active sunscreen ingredients, their concentration and their spectrum of activity. However, the Committee noted that there remains a lack of evidence to support a specific formulation or formulations. The Committee noted that the absence of a specific recommended formulation presents a challenge, as the Model Lists are intended to guide procurement by identifying products available on the market. This gap limits the ability of the Model Lists to fulfill one of their core functions in supporting standardized selection and supply.

The Committee noted that regular sunscreen use has been found to be a cost-effective intervention, with treatment costs offset by reduced costs for medical treatment of skin cancers, particularly in high-risk populations. However, the Committee acknowledged that affordability and access to broad-spectrum sunscreen products are still major barriers in many resource-constrained settings. The Committee considered that inclusion of sunscreen on the Model Lists could help to promote improved affordability and access by facilitating pooled procurement, attracting donor support and including sunscreen in universal health coverage schemes.

Based on these considerations, the Expert Committee recommended the inclusion of therapeutic broad-spectrum topical sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism. The Committee recognized the higher susceptibility to the harmful effects of UV radiation, including (but not limited to) non-melanoma skin cancer, among people with albinism and the therapeutic need for effective and safe sun protection products in this population. Therapeutic broad-spectrum sunscreens should contain proven active ingredients in appropriate amounts to absorb or filter UVA and UVB radiation and have a high SPF. The Committee was not able to recommend specific formulations for listing at this time. The Committee considered that listing sunscreens, even without a preferred formulation, was important to stimulate greater investment in research to compare and identify among the various formulations available those with a better profile. The Committee invited the submission of proposals outlining optimal formulation specifications for future consideration by the Expert Committee.

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Section 15: Antiseptics and disinfectants

15.1 Antiseptics

15.2 Disinfectants

Hypochlorous acid – addition – EML and EMLc

Hypochlorous acid **ATC code: not available**

Proposal

Addition of hypochlorous acid to the core list of the EML and EMLc for use in disinfection, antisepsis and wound decontamination.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

13. Dermatological medicines

15.1 Antiseptics

15.2 Disinfectants

Dose form(s) & strengths(s)

Solution (aqueous): ≥ 150 parts per million of hypochlorous acid

Core/complementary

Core

Individual/square box listing

Individual

Background

Hypochlorous acid solution and hydrogel were considered for inclusion on the Model Lists for use in wound management in 2017. The Expert Committee did not recommend listing because of inadequate evidence, noting that the quality

of the evidence presented in the application for the solution formulation was uncertain and that no evidence was presented for the hydrogel formulation (*1*).

An application for the inclusion of hypochlorous acid solution on the Model Lists for indications of disinfection, antisepsis and wound care (submitted by Briotech Inc., a manufacturer of hypochlorous acid products) was considered by the Expert Committee in 2021 (*2*). The current application appears to be modified version of the 2021 application.

In consideration of the 2021 version of the application, the Expert Committee noted that recommendations for chlorine-based products, including hypochlorite formulations, are included in the 2020 WHO guidance on cleaning and disinfection of environmental surfaces in the context of coronavirus disease 2019 (COVID-19). Liquid, solid or powdered hypochlorite-based formulations dissolve in water to create a dilute aqueous chlorine solution in which the undissociated hypochlorous acid is the active antimicrobial compound. The Committee noted that the Model Lists already listed chlorine-based compounds as disinfectants (Section 15.2), with a square box intended to indicate that various formulations could be considered acceptable alternatives for national selection and use. However, the listing at that time did not specify the characteristics of the alternative formulations. In consideration of a separate application to the 2021 meeting, in which square box listings in the EML and EMLc were reviewed, the Expert Committee recommended that the listing for chlorine-based compounds should be amended to provide greater clarity and guidance for countries. This recommendation resulted in liquid, powder and solid chlorine-based compounds of 0.1% available chlorine (for solution) being specified in the listing as alternatives available for national selection and use. Therefore, the Committee considered that a separate listing of hypochlorous acid solution as a disinfectant was not necessary, as this product would be captured under the amended listing for chlorine-based compounds.

With regard to hypochlorous acid for antisepsis, the Committee noted that it appeared to be effective, with a broad activity against a wide range of pathogens, and it had an acceptable safety profile. Recent advances in manufacturing have improved standardization of the product. However, the evidence supporting these considerations was relatively limited and derived from small and heterogeneous studies. The Committee noted that ongoing studies had the potential to better clarify the advantages of hypochlorous acid and would inform a future consideration of this product for inclusion on the Model Lists. The Committee therefore did not recommend the inclusion of hypochlorous acid for antisepsis and wound decontamination in 2021 but advised that it would welcome a future application with data from ongoing studies and a more comprehensive review of the literature.

Public health relevance

The public health relevance of disinfectant and antiseptic interventions are well recognized. They contribute to ensuring appropriate infection prevention and control measures and can contribute towards combatting antimicrobial resistance.

Summary of evidence: benefits

No new evidence of the benefits of hypochlorous acid solution was presented in the current application compared with the 2021 application. The following summary is reproduced from the technical report of the 2021 Expert Committee meeting (2).

Disinfection

An in vitro study showed anti-prion activity of hypochlorous acid solution using both intracerebral infectivity of treated prions of scrapie and with an in vitro fluorescent chemistry method showing efficacy against bovine spongiform encephalopathy, Creutzfeldt–Jakob disease and chronic wasting disease prions (3). Efficacy was shown to reach a log removal value of almost 6 after exposures of 60 minutes at room temperature. Log removal values of up to 3–4 were achieved with 5 minutes of contact with hypochlorous acid. Efficacy was also demonstrated against *Bacillus* spores.

A retrospective, single-institution cohort study evaluated the efficacy of universal skin decolonization using mupirocin and hypochlorous acid solution to decrease health-care associated methicillin-resistant staphylococcus aureus (MRSA) infections in patients admitted to a burn intensive care unit in a tertiary care community hospital (4). Global MRSA infection rates per 1000 patient days were 7.23 pre-intervention and 2.37 post-intervention (incidence rate ratio 0.328, 95% confidence interval (CI) 0.167 to 0.646). The patients without universal decolonization had 3.05 times higher risk of acquiring an MRSA infection than those with universal decolonization. No complications were noted from use of hypochlorous acid solution for skin decolonization.

An in vitro study to determine the efficacy of exposure to a pure hypochlorous acid solution for inactivation of high-risk human papillomavirus (HPV 16 and 18) found hypochlorous acid to be a highly effective disinfectant including with short contact times (5). All hypochlorous acid treatment times produced > 99.99% reduction in infectivity of HPV16 and HPV18, comparable to the efficacy of 0.87% sodium hypochlorite.

Antisepsis

A randomized controlled trial with 111 patients on intraperitoneal dialysis evaluated the efficacy and safety of a super-oxidized solution versus povidone-

iodine following catheter placement in reducing the frequency of dialysis-associated infections (*6*). After 8 weeks of follow-up, 24.6% of the povidone-iodine group had experienced catheter-related infections compared with 5.6% in the super-oxidized solution group ($P < 0.05$). Additionally, the mean time for resolution of infection in the povidone-iodine group was 12 days compared with 4 days in the super-oxidized solution group ($P < 0.05$).

An in vivo and vitro study assessed the effectiveness of a hypochlorous acid-based wound cleanser compared to other cleansers (povidone-iodine and chlorhexidine) in disrupting MRSA and *Pseudomonas aeruginosa* biofilms. The study also evaluated bioburden reduction of venous stasis wounds by the different cleansers (*7*). All the agents tested significantly neutralized MRSA and *P. aeruginosa* biofilms compared with saline control. Undiluted hypochlorous acid was significantly less cytotoxic than 1% and 10% povidone-iodine and chlorhexidine wound solution. No significant difference was seen in bacterial reduction in wounds after treatment with hypochlorous acid for any type of bacteria examined. In wounds treated with hypochlorous acid or chlorhexidine, similar percentage reductions were observed in bacterial colony-forming units from pre-cleansing levels when plated on tryptic soy, MacConkey, streptococcal and mannitol salt agar plates. Plates treated with chlorhexidine showed greater bacterial reduction on non-selective and gram-negative agars, whereas plates treated with hypochlorous acid showed greater bacterial reduction in *Streptococcus*-selective agars.

A randomized controlled trial in 80 patients with peritonitis compared 1-hour gastric lavage with intraperitoneal lavage with a super-oxidized solution after surgery (*8*). Purulent discharge occurred in 20.0% of patients receiving super-oxidized solution lavage versus 52.5% of patients receiving saline lavage ($P < 0.01$). The incidence of burst abdomen in patients receiving the super-oxidized solution lavage was significantly lower than those receiving saline lavage (27.5% versus 47.5%; $P < 0.05$).

A prospective randomized trial of 178 patients compared the effectiveness of a neutral pH super-oxidized hypochlorous acid solution irrigation and povidone-iodine irrigation in reducing the incidence of sternotomy wound infection following coronary artery bypass graft surgery (*9*). Sternotomy wound infection was reported in 5.7% of patients in the hypochlorous acid group and 15.6% of patients in the povidone-iodine group ($P < 0.033$).

A randomized study of 100 patients undergoing exploratory laparotomy for peritonitis compared intraoperative peritoneal lavage with a super-oxidized solution and normal saline (*10*). Surgical site infection occurred in 14% of patients receiving super-oxidized solution lavage versus 40% of patients receiving saline lavage ($P = 0.003$). Two patients in the super-oxidized solution lavage group died, compared with eight in the saline lavage group.

Wound care

A randomized trial of 60 patients compared the efficacy of hypochlorous acid versus povidone-iodine as a wound-care agent in septic traumatic wounds (*11*). Outcome measures for wound pain (no pain at day 14), odour (no odour at day 14), discharge (serous discharge at day 14) and bacterial count (reduction in day 14 quantitative count) all significantly favoured the hypochlorous acid group. At day 14, 90% of the group treated with hypochlorous acid had wounds ready for surgical reconstruction, compared with 0% in the povidone-iodine group.

A randomized trial of 60 patients compared the efficacy of dressings with hypochlorous acid and povidone iodine in the management of infected diabetic ulcers (*12*). The mean change in ulcer area was significantly higher in patients treated with hypochlorous acid dressings compared with povidone-iodine dressings (2215 mm^2 versus 1641 mm^2, $P = 0.024$). Similarly, the mean percentage reduction in ulcer area in patients receiving hypochlorous acid dressings was significantly higher (58.9% versus 40.9%, $P = 0.024$).

A randomized, prospective, multicentre, open-label pilot study tested the efficacy of topical hypochlorous acid for wound care versus oral levofloxacin versus combined therapy in 67 patients with mild diabetic foot infections (*13*). The clinical success rate 14 days after completion of therapy (test of cure) for patients treated with hypochlorous acid alone was 93.3% versus 56.3% for levofloxacin + saline-treated patients. The study was not statistically powered, but the high clinical success rate (93.3%) and the p-value ($P = 0.033$) suggest a meaningful difference.

A randomized case–control trial of 100 patients with a variety of wounds compared the efficacy and outcomes of dressings saturated in superoxide solution (Group A) or in povidone-iodine (Group B) (*14*). The most common infecting organism isolated was *P. aeruginosa*, followed by *Staphylococcus aureus* and *Klebsiella* spp. The decrease in surface area of wounds at the end of 1, 2, 3 and 4 weeks, was statistically significantly greater in Group A than Group B ($P = 0.005$, $P = 0.002$, $P < 0.001$ and $P = 0.001$, respectively).

A randomized controlled trial examined the efficacy and safety of a super-oxidized solution compared with povidone-iodine (as adjuncts to systemic antibiotics and debridement as needed) in the management of wide (> 5 cm) post-surgical lesions of the diabetic foot in 40 patients with post-surgical wounds (*15*). Healing, as measured by complete re-epithelization, occurred in 90% of the patients treated with super-oxidized solution compared with 55% in the povidone-iodine group ($P < 0.01$). The group treated with super-oxidized solution also had fewer episodes of reinfection ($P < 0.01$).

In a retrospective analysis of a cohort of 897 patients with 1249 venous leg ulcers treated with hypochlorous acid solution, all the ulcers healed completely (*16*). Treatment involved cleaning and debriding foreign matter, debris and necrotic

material via application of hypochlorous acid solution, with or without pressure and abrasion using hypochlorous acid-soaked sterile gauze. Sharp debridement was performed where required within 10 days of presentation. All ulcers were dressed and/or loosely packed with hypochlorous acid-soaked sterile gauze. Compressive bandaging was applied. Light abrasion using sterile gauze and flushing with hypochlorous acid solution were done every few days. Longest healing times were observed in 10 patients for whom compression therapy was contraindicated. However, aggressive management adding hypochlorous acid resulted in complete wound closure within 180 days for this treatment-refractory group (*16*).

A randomized, single-blind trial studied the effect of standard of care with or without neutral pH super oxidized solution in the treatment of 45 patients with diabetic foot ulcers (*17*). Odour reduction was reported in 100% of patients treated with super-oxidized solution, compared with 20% in the standard care group. Surrounding cellulitis diminished in 80.5% versus 43.7% of patients and advancement to the granulating tissue stage in 90.4% versus 62.5% of patients were observed in the super-oxidized and standard care groups, respectively.

One hundred patients with diabetic foot ulcer wounds were randomized to treatment with either daily super-oxidized water (hypochlorous acid) or saline-soaked gauzes (*18*). Patients treated with hypochlorous acid had a significantly shorter period of hospitalization than saline-treated patients: 1–7 days hospitalization for 68% of patients treated with hypochlorous acid versus for 20% treated with saline-soaked gauzes; $P < 0.05$). A higher proportion in the hypochlorous acid group experienced a down-grading of their ulcers (62% versus 15%; $P < 0.05$).

A study prospectively randomized 200 patients with different types of wounds to treatment with either gauze saturated in hypochlorous acid or in povidone-iodine and with antibiotics (*19*). After a mean follow-up of 21 days, the average reduction in the wound size of diabetic foot ulcer in the hypochlorous acid group was 70% compared with 50% in the povidone iodine group. Earlier granulation and epithelization were seen in the wounds treated with hypochlorous acid solution compared with those treated with povidone-iodine (100% versus 85% at day 18).

Summary of evidence: harms

No new evidence for safety of hypochlorous acid solution was presented in the current application compared with the 2021 application. The following summary is reproduced from the technical report of the 2021 Expert Committee meeting (*2*).

Clinical adverse events from exposure to pure hypochlorous acid (present at a pH between 4.0 and 5.33) have not been recorded in the medical literature. However, reports of incidents following exposure to relatively high pH, crude formulations (>6.5) containing mixed oxidants, including hypochlorite, have occurred due to poorly controlled manufacturing processes.

Eye and skin inflammation and respiratory irritation are common with hypochlorite (bleach), which can be present at levels of 30% or more in hypochlorous acid solutions made or adjusted to pH 7 or in swimming pools that are improperly managed and allow pH to rise into the alkaline range.

A 2011 study evaluated the risk of biological toxicity in a mouse model when hypochlorous acid was ingested as drinking water for 8 weeks. Hypochlorous acid had no systemic effects in that animal model and the authors concluded it would be safe if used as a mouthwash, even if ingested (*20*).

Another study using an animal model looked at the potential toxicity of infusions of hypochlorous acid into the intraperitoneal cavity of rats. No statistical difference in blood biochemistry, renal function or liver function was found in rats infused with hypochlorous acid (*21*).

A review of hypochlorous acid versus normal saline as a peritoneal lavage to prevent post-surgical infections after perforated appendicitis in children found no evidence of toxicity associated with hypochlorous acid (*22*).

Environmental safety

Hypochlorous acid is a highly reactive molecule and short-lived when exposed to pathogens or another bioload. On exposure, pure hypochlorous acid degrades within minutes to sodium chloride and water, becoming benign and non-reactive saltwater closely analogous to human tears (*23*). Because of that rapid reactivity, pure hypochlorous acid at a label concentration of 180 ppm poses no risk of environmental contamination (except as a mild 0.9% salt solution) and does not require personal protective equipment, can be stored with no hazardous materials protocol and can be disposed of with no risk of generating a toxic waste stream.

In contrast, impure hypochlorous acid/hypochlorite solutions, such as hypochlorite (bleach), require personal protective equipment and hazardous material storage, and must be disposed of as both a toxic materials risk and an environmental hazard. Those same hazard considerations also apply to other classes of antisepsis and disinfection agents.

Additional evidence

–

WHO guidelines

WHO interim guidance on cleaning and disinfection of environmental surfaces in the context of COVID-19 (*24*) states that the selection of disinfectants should take into account: the microorganisms targeted; the recommended concentration and contact time; compatibility of chemical disinfectants and surfaces being disinfected; toxicity; ease of use; and product stability. Hypochlorite-based products include liquid (sodium hypochlorite), solid or powdered (calcium

hypochlorite) formulations. These formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid is active as the antimicrobial compound.

Costs/cost–effectiveness

No cost–effectiveness data were presented in the application.

The application stated that current product pricing at scale can probably be achieved at less than 1 euro per wholesale litre, with minor regional variations based on water, salt and energy costs.

Availability

The application stated that production of hypochlorous acid in local manufacturing facilities is routine and has the advantage of eliminating the cost of transport. Proprietary products are also available.

Other considerations

–

Committee recommendations

The Expert Committee noted that the current application was a slightly modified version of an application for hypochlorous acid solution submitted by Briotech, Inc. in 2021. The Committee noted that no new evidence of benefits and harms of hypochlorous acid solution was presented, only the evidence already evaluated by the 2021 Expert Committee.

The Committee recalled the recommendations of the 2021 Expert Committee, and considered that in the absence of new evidence, it was not possible to reach different conclusions. The Committee therefore did not recommend the inclusion of hypochlorous acid solution for topical use in antisepsis and would care because of inconclusive evidence for benefit. In reviewing the case for disinfection, the Committee agreed that an independent listing for hypochlorous acid solution as a disinfectant, separate to the existing listing for chlorine-based compound, would be beneficial to enhance understanding of differences between hypochlorite products and hypochlorous acid.

The Expert Committee therefore recommended that an explicit listing for hypochlorous acid solution as an environmental disinfectant be included on the EML and EMLc to aid differentiation between hypochlorite and hypochlorous acid products.

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Section 18: Medicines for endocrine disorders

18.1 Adrenal hormones and synthetic substitutes

Prednisolone – new indication – EML and EMLc

Prednisolone **ATC code: H02AB06**

Proposal

Inclusion of prednisolone 1 mg tablets on the core list of the EML and EMLc for the new indication for treatment of adults and children with primary and secondary adrenocortical insufficiency, and slow withdrawal of prednisolone in corticosteroid-induced adrenal suppression.

Applicant

Karim Meeran, Imperial College Faculty of Medicine, London, United Kingdom of Great Britain and Northern Ireland

WHO technical department

The Department of Maternal, Newborn, Child and Adolescent Health and Ageing reviewed and provided comments on the application. The technical department supported the inclusion of prednisolone only on the EML for treatment of adults. They did not support the inclusion of prednisolone on the EMLc for use in children due to its long-acting nature and the potential for adverse effects on growth.

EML/EMLc

EML and EMLc

Section

18.1 Adrenal hormones and synthetic substitutes

Dose form(s) & strengths(s)

Tablet: 1 mg

Core/complementary

Core

Individual/square box listing

Square box listing for prednisolone with prednisone as a therapeutic alternative.

Background

Prednisolone has not previously been considered for inclusion on the Model Lists for the proposed indication. However, prednisolone 5 mg and 25 mg tablets and 5 mg/mL oral liquid are included on the Model Lists for other indications.

Fludrocortisone 100 microgram tablets and hydrocortisone 5 mg, 10 mg and 20 mg tablets for use in adrenal insufficiency have been included on the EML and EMLc since 2009. At that time, the Expert Committee considered the findings of one small study of nine patients that compared hydrocortisone and prednisolone in the management of congenital adrenal hyperplasia. This study showed that prednisone was associated with significantly greater adverse effects on growth than hydrocortisone. It was acknowledged that the use of other glucocorticoids such as dexamethasone and prednisolone was generally avoided in children due to adverse effects on growth (*1*).

Public health relevance

Primary adrenal insufficiency (Addison disease) has an estimated worldwide prevalence of 1 in 10 000 people. Causes include autoimmune-mediated adrenal failure, tuberculosis and infectious diseases. Secondary adrenal insufficiency has an estimated worldwide prevalence of 1 in 4000 people and is caused by adrenocorticotropic hormone deficiency due to hypothalamic-pituitary disease. It is often associated with other pituitary hormone deficiencies. Tertiary adrenal insufficiency (glucocorticoid-induced adrenal suppression) is the most common form, affecting up to 1 in 100 people worldwide who are on long-term glucocorticoid therapy at doses that cause adrenal suppression (*2*–*4*).

Patients with adrenal insufficiency require lifelong glucocorticoid replacement therapy to manage their condition. The traditional treatment involves hydrocortisone, which is administered multiple times a day. Adrenal insufficiency is associated with increased mortality despite glucocorticoid replacement therapy, with a standardized mortality ratio > 2 (*5*).

Summary of evidence: benefits

The application described having reviewed the evidence considered in the development of the United Kingdom's National Institute for Health and Care Excellence (NICE) guideline *Adrenal insufficiency: identification and management* (*6*) . The evidence review included six randomized controlled trials in adults with primary adrenal insufficiency which included comparisons of different formulations and dosing of hydrocortisone and standard care. None of the included studies included prednisolone. The evidence review included five randomized controlled trials that investigated the effect of oral glucocorticoids (hydrocortisone, prednisolone and dexamethasone) at different doses and

dosing schedules in the management of congenital adrenal hyperplasia. One trial compared once daily prednisolone to three times daily hydrocortisone in 44 prepubertal and pubertal participants with 21-hydroxylase deficiency (7). After 1 year, participants taking daily prednisolone (2.4 to 3.5 mg/m^2) showed stable bone maturation ratio, growth velocity and height gains compared with those taking three times daily hydrocortisone (10–15 mg/m^2). The evidence review included four randomized controlled trials that compared different doses of oral hydrocortisone in adults with secondary adrenal insufficiency. No studies in children or people with tertiary adrenal insufficiency were identified.

A retrospective observational study evaluated the cardiovascular risk profiles of prednisolone and hydrocortisone in the United Kingdom (8). Data from participants receiving prednisolone once daily ($n = 64$) or hydrocortisone three times daily ($n = 82$) as glucocorticoid replacement therapy for primary or secondary adrenal insufficiency were analysed. The mean daily dose was 3.7 mg and 20.5 mg for prednisolone and hydrocortisone, respectively. Results showed no significant differences between prednisolone and hydrocortisone for most cardiovascular risk factors including in total cholesterol (4.77 mmol/L versus 5.15 mmol/L; $P = 0.07$), low-density lipoprotein levels (2.75 mmol/L versus 2.90 mmol/L; $P = 0.45$), systolic (127 mmHg versus 129 mmHg) or diastolic (77 mmHg versus 79 mmHg; $P = 0.19$) blood pressure. Patients receiving prednisolone had a significantly lower waist-to-hip ratio (0.92 versus 0.95; $P < 0.05$). Patient satisfaction ratings were significantly higher in the prednisolone group.

A 2016 study examined the pharmacokinetic profile of prednisolone in six patients with secondary adrenal insufficiency and three healthy volunteers (9). The mean prednisolone dose required for adequate replacement in patients with adrenal insufficiency was 3.86 mg. The mean maximal serum concentration (C_{max}) was 114.0 microgram/L, with peak concentration at 1.43 hours. The pharmacokinetic profile of prednisolone was found to be similar to the published profile of a dual-release hydrocortisone formulation, suggesting that once-daily prednisolone can be used as an effective and lower-cost alternative to hydrocortisone.

Summary of evidence: harms

The ongoing retrospective observational HYPER-AID study is comparing anthropometric, biochemical and subjective health outcomes between hydrocortisone and prednisolone in adults with adrenal insufficiency switching from one treatment to the other (10). Interim results from different study centres in the United Kingdom have been published in abstract form. At one tertiary care centre, 13 of 15 recruited patients completed the switch from hydrocortisone to prednisolone (11); 14 (92.3%) had secondary adrenal insufficiency. Results

showed minor but statistically significant decreases in mean body mass index (from 31.56 kg/m^2 to 30.87 kg/m^2; $P = 0.02$) and waist circumference (from 106.11 cm to 103.26 cm; $P = 0.01$). No significant differences were observed in other cardiovascular or metabolic markers. Results from another centre reported that among 23 patients, 11 switched from prednisolone to hydrocortisone and experienced significant weight gain of 3.2 kg ($P < 0.004$) (*12*). Results from other centres have reported varying effects of switching from hydrocortisone to prednisolone in terms of weight, body mass index and waist circumference. In general, cardiovascular markers showed no significant differences (*13*, *14*).

A 2017 multicentre study evaluated risk factors for cardiovascular disease in patients with adrenal insufficiency receiving prednisolone ($n = 50$) or hydrocortisone ($n = 909$) using real-world data from the European Adrenal Insufficiency Registry (EU-AIR) (*15*). The results showed significantly higher mean total cholesterol (6.3 mmol/L versus 5.4 mmol/L; $P = 0.003$) and low-density lipoprotein levels (3.9 mmol/L versus 3.2 mmol/L; $P = 0.013$) in patients receiving prednisolone compared with those receiving hydrocortisone at baseline and at follow-up. Glycated haemoglobin (HbA1c), high-density lipoprotein, triglyceride levels, body mass index, systolic and diastolic blood pressure, and waist circumference were not significantly different between treatment groups.

Additional evidence

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WHO guidelines

WHO guidelines for the management of adrenal insufficiency are not currently available.

The NICE guidelines for adrenal insufficiency include recommendations for the use of prednisolone in children younger than 16 years (if they have stopped growing) and people older than 16 years with primary adrenal insufficiency, congenital adrenal hyperplasia and secondary and tertiary adrenal insufficiency as an alternative glucocorticoid to first-choice hydrocortisone. Prednisolone is not recommended as replacement therapy for adrenal insufficiency in children younger than 1 year. The guidelines also include recommendations for prednisolone dose-tapering and withdrawal which incorporates 1 mg dose reductions to avoid adrenal crisis and glucocorticoid withdrawal syndrome (*16*).

Costs/cost–effectiveness

No cost–effectiveness information was presented in the application.

The application reported available prices of prednisolone and hydrocortisone tablets in a variety of settings.

In Australia, prednisolone 1 mg tablets cost 16.56 Australian dollars (AU$) for 100 tablets, sufficient for 1 month supply at 3 mg a day. Hydrocortisone 4 mg tablets cost AU$ 42.39 for 100 tablets or AU$ 63.58 a month for a typical dosing regimen.

In Pakistan, prednisolone 5 mg tablets cost between 45–110 Pakistani rupees (P Rs) a month. Hydrocortisone costs range from P Rs 252 for generic hydrocortisone to P Rs 5300–10 500 for branded hydrocortisone.

In Sri Lanka, prednisolone 5 mg tablets cost between 3 and 14 Sri Lankan rupees (SL Rs) a day. Generic branded hydrocortisone 20 mg tablets (used to deliver divided daily doses) cost between SL Rs 64 and SL Rs 96 a day.

In Thailand, prednisolone is reported to be generally more affordable than hydrocortisone, however specific price information was not provided.

In the United Kingdom, prednisolone 1 mg tablets cost 0.71 pounds sterling (£) a month at a dose of 1 mg daily, and £2.13 a month at a dose of 3 mg daily. Hydrocortisone 10 mg tablets cost £3.84 a month for a typical dosing regimen, with lower strength tablets available at higher costs.

Availability

Prednisolone 1 mg tablets are available in a limited number of countries, including Australia, New Zealand and United Kingdom. They are reported to be unavailable in Pakistan, Sri Lanka and Thailand and other countries within the Association of Southeast Asian Nations.

Prednisone 1 mg tablets are available in Australia and the United States of America.

Other considerations

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Committee recommendations

The Expert Committee recognized the public health relevance of effective treatments for adrenal insufficiency and noted that fludrocortisone and hydrocortisone are currently included on the Model Lists for this indication.

The Committee considered that the available evidence, while low-quality, supported the effectiveness of prednisolone in the treatment of adrenal insufficiency. Further, the evidence suggests that prednisolone may offer some advantages over hydrocortisone in terms of impact of treatment on weight, bone metabolism and cardiovascular outcomes. The Committee considered that low-dose prednisolone (i.e. 3 mg to 4 mg daily) was generally safe for the treatment of adrenal insufficiency. Documented harms of prednisolone are usually associated with higher doses. Overall, the Committee considered that the balance of benefits to harms was acceptable.

The Committee noted that no evidence on cost–effectiveness was presented in the application, but that the price of prednisolone tends to be lower than the price of hydrocortisone in most settings. The Committee considered that the reduced impact on budgets of using prednisolone instead of hydrocortisone would be particularly relevant in resource-constrained settings.

The Committee noted that the current availability of the 1 mg tablet formulation of prednisolone is limited. The Committee considered that its inclusion on the Model Lists could catalyse actions to improve availability and access.

The Expert Committee therefore recommended the inclusion of prednisolone 1 mg tablets on the core list of the EML and EMLc for the treatment of adults and children with adrenal insufficiency. Listing is recommended for prednisolone with a square box, specifying prednisone 1 mg as a therapeutic alternative.

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18.5 Medicines for diabetes

18.5.1 Insulins

Insulin, analogue long-acting – new formulation – EML and EMLc

Insulin degludec	**ATC code: A10AE06**
Insulin detemir	**ATC code: A10AE05**
Insulin glargine	**ATC code: A10AE04**

Proposal

Addition of 10 mL vial formulations of long-acting insulin analogues (insulin degludec, insulin detemir and insulin glargine) to the core list of the EML and EMLc for the treatment of diabetes.

Applicant

ACCISS Study (Addressing the Challenge and Constraints of Insulin Sources and Supply), Health Action International

WHO technical department

The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed the application and supported the inclusion of long-acting insulin analogue 10 mL vial formulations on the Model Lists.

EML/EMLc

EML and EMLc

Section

18.5.1 Insulins

Dose form(s) & strengths(s)

Injection: 100 IU/mL in 10 mL vial

Core/complementary

Core

Individual/square box listing

Square box

Background

Long-acting insulin analogues were added to the EML and EMLc in 2021 as 3 mL cartridges or prefilled pen formulations containing 100 IU/mL.

Public health relevance

The public health relevance of insulin for the treatment of type 1 and type 2 diabetes mellitus is well established.

Summary of evidence: benefits

Evidence for the benefits of long-acting insulin analogues was evaluated in 2021.

Summary of evidence: harms

Evidence for the harms of long-acting insulin analogues was evaluated in 2021.

Additional evidence

–

WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes include a weak recommendation (moderate-quality evidence) to consider using long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (*1*). In developing the guidelines, studies of comparisons of preferences between various insulin injection devices were excluded.

The WHO guidelines for the management of type 1 diabetes in children are expected to be available in 2025.

Costs/cost–effectiveness

The application reported that limited data were available on price differences between long-acting analogues in vials, prefilled pens and cartridges in low- and middle-income countries. In private pharmacies in Peru in 2022, the median price of 1000 IU of insulin glargine in vials was 47.72 United States Dollars (US$) and in prefilled pens was US$ 70.39 (an increase of 48%). Similar findings were found in 2023. In Vietnam in 2022, the median price of 1000 IU of insulin glargine in vials was US$ 22.30 and in prefilled pens was US$ 42.51.

Availability

Long-acting insulin analogues in 10 mL vials have wide global marketing approval.

Insulin glargine in 10 mL vials is prequalified by WHO.

Other considerations

–

Committee recommendations

The Expert Committee recognized the importance of affordable and equitable access to insulin products as a public health priority.

The Committee considered that the inclusion of long-acting insulin analogues in 10 mL vials on the Model Lists would provide an additional formulation choice and delivery option for people with diabetes who use these insulins and would be consistent with the current listings for human insulins on the Model Lists.

The Committee therefore recommended that the listings for long-acting insulin analogues on the EML and EMLc be extended to include 10 mL vial formulations containing 100 IU/mL.

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Insulin, analogue rapid-acting – addition – EML and EMLc

Insulin analogues, rapid-acting	
Insulin aspart	**ATC code: A10AB05**
Insulin glulisine	**ATC code: A10AB06**
Insulin lispro	**ATC code: A10AB04**

Proposal

Addition of rapid-acting insulin analogues in the core list of the EML and EMLc for the treatment of patients with type 1 and type 2 diabetes mellitus who are at high risk of experiencing hypoglycaemia with human insulin, and for treatment of diabetes mellitus in pregnancy (i.e. gestational diabetes).

Applicant

T1International

WHO technical department

The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical department did not support the inclusion of rapid-acting insulin analogues on the Model Lists because of limitations in the evidence for benefits and the high costs of the medicines.

EML/EMLc

EML and EMLc

Section

18.5.1 Insulins

Dose form(s) & strengths(s)

Injection solution: 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or prefilled pen

Core/complementary

Core

Individual/square box listing

Square box listing for insulin lispro, with insulin aspart and insulin glulisine (including quality-assured biosimilars) as specified therapeutic alternatives.

Background

Rapid-acting insulin analogues have not previously been evaluated for inclusion on the Model Lists.

The Model Lists currently include human insulin (short- and intermediate-acting) and long-acting insulin analogues.

Public health relevance

The public health relevance of insulin in the treatment of diabetes is well established.

According to data from the Global Burden of Disease study, diabetes mellitus affected 525.6 million people globally in 2021. Most cases were type 2 diabetes (506 million). The disease was responsible for more than 1.6 million deaths and 2.7% of global disability-adjusted life years (*1*). A 2021 study estimated the global prevalence of gestational diabetes to be 14.0% (*2*).

Summary of evidence: benefits

Type 1 diabetes

A 2016 Cochrane systematic review of nine randomized controlled trials (2693 participants) assessed the effects of rapid-acting insulin analogues versus regular human insulin in non-pregnant adults with type 1 diabetes (*3*). Six studies involved insulin lispro and three studies involved insulin aspart. For the secondary outcome of glycaemic control, the mean difference (MD) in glycated haemoglobin (HbA1c) favoured rapid-acting insulin analogues (MD −0.15% (95% confidence interval (CI) −0.21% to −0.08%; nine randomized controlled trials, 2608 participants; low-quality evidence). No data on all-cause mortality or micro- and macrovascular complications were reported in the trials.

A 2018 systematic review and meta-analysis assessed the efficacy and safety rapid-acting insulin analogues in children and adolescents (five randomized controlled trials) and people using continuous subcutaneous insulin infusion (six randomized controlled trials) with type 1 diabetes (*4*). The review also identified seven randomized controlled trials in pregnancy, but these were not included in the quantitative meta-analysis due to heterogeneity. Among children and adolescent trials, no significant difference was found between rapid-acting insulin analogues and regular human insulin for severe hypoglycaemic events (risk difference (RD) 0.00, 95% CI −0.01 to 0.01; five randomized controlled trials, 1216 participants). Among the trials on continuous subcutaneous insulin infusion, rapid-acting insulin analogues led to greater lowering of postprandial plasma glucose than regular human insulin (MD −1.63 mmol/L, 95% CI −1.71 to −1.54 mmol/L,; five randomized controlled trials, 460 participants), but no significant differences were found between treatment groups for fasting plasma glucose (MD −0.53 mmol/L, 95% CI −1.21 to 0.15 mmol/L; three randomized

controlled trials, 324 participants), severe hypoglycaemic episodes (RD −0.01, 95% CI −0.04 to 0.02; seven randomized controlled trials, 553 participants), the rate of any hypoglycaemic episode (RD −0.75, 95% CI −2.21 to 0.72; five randomized controlled trials 232 participants) or difference in HbA1c (MD −0.19%, 95% CI −0.46% to 0.08%; five randomized controlled trials, 451 participants).

A 2019 systematic review and meta-analysis of 22 randomized controlled trials (6235 participants) evaluated the effects of rapid-acting insulin analogues versus regular human insulin in children, adolescents and adults with type 1 diabetes (*5*). Primary outcomes were hypoglycaemia and postprandial glucose levels. HbA1c and quality of life were secondary outcomes. Rapid-acting insulin analogues were associated with lower postprandial glucose levels (MD −19.44 mg/dL, 95% CI −21.49 to −17.39; 15 randomized controlled trials, 5031 participants) compared with regular human insulin. For the outcome of HbA1c, pooled data from 15 randomized controlled trials (5204 participants) showed insulin aspart and insulin lispro to be associated with lower HbA1c levels compared with regular human insulin (MD −0.13%, 95% CI −0.16% to −0.10%). However, when assessed separately, only insulin aspart was associated with lower HbA1c compared with regular human insulin.

Type 2 diabetes

A 2018 Cochrane systematic review of 10 randomized controlled trials (2751 participants) assessed the effects of rapid-acting insulin analogues versus regular human insulin in non-pregnant adults with type 2 diabetes (*6*). For the primary outcome of all-cause mortality, mortality events were rare but occurred more frequently in the insulin analogue group (0.4% versus 0.2%, Peto odds ratio (OR) 1.66, 95% CI 0.47 to 6.64; three randomized controlled trials, 2519 participants; moderate-certainty evidence). No differences were observed between different types of insulin analogues nor between treatment groups for severe hypoglycaemic events (outcomes not meta-analysed). For the secondary outcome of glycaemic control, no significant difference was seen between treatment groups in the change in HbA1c (MD −0.03%, 95% CI −0.16% to 0.09%); nine randomized controlled trials, 2608 participants; low-certainty evidence), with no differences observed between different types of insulin analogues.

Pregnant women with pre-existing diabetes and gestational diabetes

A 2017 Cochrane systematic review of five randomized controlled trials (554 women and babies) evaluated different insulin types and regimens in pregnant women with pre-existing type 1 or type 2 diabetes (*7*). Two of the included trials compared rapid-acting insulin analogues with regular human insulin, only one of which reported on outcome measures of interest of the review. For the main comparison of insulin lispro versus regular human insulin (one randomized

controlled trial, 33 participants), there was very-low-quality evidence of no significant differences between treatment groups for perinatal death (relative effect not estimable), preeclampsia (risk ratio (RR) 0.68, 95% CI 0.35 to 1.30), caesarean section (RR 0.59, 95% CI 0.25 to 1.39) and birth trauma (relative effect not estimable).

The 2018 systematic review that assessed efficacy and safety of rapid-acting insulin analogues in special populations with type 1 diabetes included two randomized controlled trials in people with pre-gestational type 1 diabetes and four randomized controlled trials in people with gestational diabetes (*4*). The results generally showed similar outcomes with rapid-acting insulin analogues and regular human insulin for glycaemic control, hypoglycaemic events and neonatal outcomes. In pregnant women with pre-existing type 1 diabetes, the largest trial randomized 322 women to receive insulin aspart or regular human insulin in combination with neutral protamine Hagedorn basal insulin and found that HbA1c levels were comparable between treatment arms at the end of the second and third trimesters. Postprandial plasma glucose increments, and mean plasma glucose levels at 90 minutes post-breakfast were significantly lower for insulin aspart. Insulin aspart was associated with a non-significant reduction in risk of major hypoglycaemic events (RR 0.72, 95% CI 0.36 to 1.46). Among trials in women with gestational diabetes, the results generally indicated insulin lispro to be at least as effective as or more effective than regular human insulin for glycaemic control.

Summary of evidence: harms

Type 1 diabetes

From the 2016 Cochrane systematic review in type 1 diabetes, for the outcome of severe hypoglycaemic episodes, rapid-acting insulin analogues were associated with a non-significant reduced risk of severe hypoglycaemia compared with human insulin (OR 0.89, 95% CI 0.71 to 1.12; seven randomized controlled trials, 2459 participants, very-low-quality evidence). For the outcome of weight gain, no significant difference was seen between treatment groups (MD −0.11 kg, 95% CI −0.25 kg to 0.04 kg; six randomized controlled trials, 2385 participants, moderate-quality evidence) (*3*).

From the 2018 systematic review in special populations with type 1 diabetes, among children and adolescent trials, no significant difference was seen between rapid-acting insulin analogues and regular human insulin for severe hypoglycaemic events (risk difference (RD) 0.00, 95% CI −0.01 to 0.01; five randomized controlled trials, 1216 participants, low-quality evidence) (*4*). Among the trials on continuous subcutaneous insulin infusion, no significant differences were seen between treatment groups for severe hypoglycaemic episodes (RD −0.01, 95% CI −0.04 to 0.02; seven randomized controlled trials,

553 participants) or any hypoglycaemic episode (RD −0.75, 95% CI −2.21 to 0.72; five randomized controlled trials 232 participants).

From the 2019 systematic review, results for all hypoglycaemic episodes per month showed no difference between rapid-acting insulin analogues and human insulin (risk rate (RR) 0.94, 95% CI 0.89 to 1.00; 22 randomized controlled trials, 6235 participants). However, in a sensitivity analysis excluding studies with a high risk of bias, rapid-acting insulin analogues were associated with fewer hypoglycaemic events per month compared with regular human insulin (RR 0.93, 95% CI 0.87 to 0.99; 20 randomized controlled trials, 6180 participants). Rapid-acting insulin analogues were associated with a reduced risk of nocturnal hypoglycaemia (RR 0.55, 95% CI 0.40 to 0.76; eight randomized controlled trials, 1995 participants) and severe hypoglycaemia (RR 0.68, 95% CI 0.60 to 0.77; 15 randomized controlled trials, 5945 participants) compared with regular human insulin (5).

Type 2 diabetes

From the 2016 Cochrane systematic review in type 2 diabetes, for the primary outcome of all-cause mortality, mortality events were rare but occurred more frequently in the insulin analogue group (0.4% versus 0.2%, Peto OR 1.66, 95% CI 0.47 to 6.64; three randomized controlled trials, 2519 participants; moderate-certainty evidence). No differences were observed between different types of insulin analogues nor between treatment groups for severe hypoglycaemic events (outcome not meta-analysed) (6).

Additional evidence

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WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes include a strong recommendation (low-quality evidence) for the use of human insulin to control blood glucose levels in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (8). The recommendation was strong because evidence of better effectiveness of insulin analogues was lacking, and human insulin had a better resource-use profile. The guidelines also include a weak recommendation to consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (moderate-quality evidence for severe hypoglycaemia) (8).

WHO guidelines for the pharmacological management of gestational diabetes or pre-existing diabetes in pregnant women are not currently available.

Costs/cost–effectiveness

The application identified and summarized the findings of 19 research articles considering cost, cost–effectiveness, budget impact and price of insulin (*9*–*27*). Most studies were conducted in high-income settings and published more than 5 years ago.

In summary, the application highlighted that rapid-acting insulin analogues are more expensive than regular human insulin in various settings, although production costs are relatively similar. The growing availability of biosimilars offers opportunities for price reductions. Despite higher upfront costs, insulin analogues may result in lower overall health-care costs due to a reduced incidence of hypoglycaemia, fewer hospitalizations and lower rates of diabetes-related complications. Cost–effectiveness studies in various settings suggest that rapid-acting insulin analogues can be cost-effective, especially for type 1 diabetes. For type 2 diabetes, the cost–effectiveness is more variable. Survey data from different countries show significant variation in the prices of rapid-acting insulin analogues. While insulin analogues are often more expensive than human insulin, increased availability of biosimilars and efforts in price negotiations may help to lower costs in the future.

Availability

Rapid-acting insulin analogues, including insulin lispro, insulin aspart and insulin glulisine, have wide global regulatory approval. Biosimilar versions of insulin aspart and/or insulin lispro are available in some settings.

Other considerations

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Committee recommendations

The Expert Committee recognized the importance of affordable and equitable access to insulin products as a public health priority.

The Committee considered that the available evidence indicates generally comparable efficacy and safety between rapid-acting insulin analogues and regular human insulin. The Committee noted that some studies provided evidence of higher patient satisfaction scores with rapid-acting insulin analogues and others suggest that rapid-acting insulin analogues may be associated with lower rates of complications, with medicine costs offset by reduced demand for high-cost treatments and health services for complications, particularly in type 1 diabetes. However, the Committee considered these benefits were tenuous and did not provide compelling arguments to support the inclusion of rapid-acting insulin analogues on the Model Lists.

The Committee recognized that rapid-acting insulin analogues may be more expensive than regular human insulin and may be less affordable in some resource-constrained settings. However, in other settings the prices of rapid-acting insulin analogues do not exceed the price of regular human insulin. The Committee noted that larger insulin markets could help stabilize prices, secure supply chains of quality-assured products and mitigate the risks of shortages. In countries where insulin prices are excessive, consideration should be given to strengthening the regulatory framework, implementing or maintaining price control, or reference-pricing mechanisms. The outcomes of price controls and reference pricing for essential medicines should be closely monitored as these policies can have unintended consequences (e.g. shortages). The Committee emphasized the importance of commitment and action from WHO, Member States, insulin producers, procurement agencies and other stakeholders to address the problem of equitable and affordable access to insulin products globally. The Committee highlighted the need for multipronged policy, pricing and procurement strategies to strengthen affordable access.

In consideration of access to insulin, the Committee noted with concern the progressive withdrawal of regular human insulin from markets. The Committee acknowledged the concerns of the WHO technical department that the inclusion of rapid-acting insulin analogues might adversely affect the ongoing availability of regular human insulin, particularly in the most resource-constrained settings. However, the Committee also noted that in the case of insulin, EML-listing was unlikely to be the strongest or most influential driver of market access nor to revive the marginal sales of human insulin. The Committee emphasized that no changes were being made to the status of human insulins on the Model Lists.

The Committee considered that the inclusion of rapid-acting insulin analogues would serve to increase the number of insulin products on the Model Lists and would complement the listing of long-acting insulin analogues for use in basal-bolus regimens. This is consistent with the listings for short- and intermediate-acting human insulins.

Based on these considerations, the Expert Committee recommended the inclusion of rapid-acting insulin analogues (insulin aspart, insulin glulisine and insulin lispro, and their quality-assured biosimilars, as therapeutic alternatives) on the core list of the EML and EMLc for the treatment of people with type 1 and type 2 diabetes, and people with gestational diabetes.

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18.5.2 Hypoglycaemic agents

Glucagon-like peptide-1 receptor agonists – addition obesity – EML

Semaglutide **ATC code: A10BJ06**

Proposal

Addition of semaglutide to the core list of the EML for the treatment of adults with obesity. Listing is proposed with a square box as the representative glucagon-like-peptide-1 (GLP-1) receptor agonist, with beinaglutide, dulaglutide, exenatide, liraglutide and the GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual agonist tirzepatide as therapeutic alternatives.

Applicant

MAGIC Evidence Ecosystem Foundation, Oslo, Norway

WHO technical department

The Department of Nutrition and Food Safety reviewed and provided comments on the application. The technical unit supported the inclusion of GLP-1 receptor agonists and GLP-1/GIP dual agonists on the EML for the treatment of adults ≥ 19 years with obesity when body mass index (BMI) is ≥ 30 kg/m^2.

EML/EMLc

EML

Section

18.5.2 Hypoglycaemic agents

Dose form(s) & strengths(s)

Injection solution: 0.68 mg/mL, 1.35 mg/mL

Tablet: 3 mg, 7 mg, 14 mg

Core/complementary

Core

Individual/square box listing

Square box, with beinaglutide, dulaglutide, exenatide, liraglutide and tirzepatide as therapeutic alternatives.

Background

An application for the inclusion of GLP-1 receptor agonists, represented by liraglutide, on the EML for the treatment of obesity in adults was considered by the Expert Committee in 2023 (*1*). The Committee noted that GLP-1 receptor agonists have been shown to reduce weight and BMI in the short term compared with placebo. However, evidence about the efficacy in different populations was lacking. The optimal duration of treatment had also not been defined since maintenance of weight reduction once therapy is stopped seems to be rare. Furthermore, it was unclear whether treatment of overweight and obesity with GLP-1 receptor agonists affects long-term clinically important outcomes such as hypertension, hyperglycaemia, osteoarthritis and mortality. The Committee also noted that the use of GLP-1 receptor agonists was associated with an increased frequency of adverse events such as nausea, vomiting, constipation and diarrhoea compared with placebo, although these were usually manageable and self-limiting. The Committee stressed the importance of long-term safety data, which were currently lacking, given the potential need for long-term administration of these medicines to maintain weight loss. The Committee noted that the prices of the medicines were currently high, and treatments were unlikely to be cost-effective in several regions. The Expert Committee therefore did not recommend the inclusion of GLP-1 receptor agonists on the EML for weight loss in people with obesity because of uncertain long-term clinical benefit and safety in this population.

Public health relevance

Obesity is an important public health challenge with many implications for health systems and society. According to WHO, in 2022, one in eight people globally was living with obesity, marking a dramatic rise in prevalence since 1990. Adult obesity has more than doubled and adolescent obesity has quadrupled during this period. In 2022, 2.5 billion adults were overweight, of whom 890 million were living with obesity, representing 43% and 16% of the global adult population, respectively. Among 390 million overweight children and adolescents aged 5–19 years, 160 million were living with obesity (*2*).

The health risks caused by overweight and obesity are well known. According to the Global Burden of Disease Study, in 2021, about 3.7 million deaths from noncommunicable diseases (e.g. cancer, cardiovascular diseases, chronic respiratory diseases, diabetes, digestive disorders and neurological disorders) were attributable to a higher-than-optimal BMI (*3*).

The economic impact of obesity is substantial. In 2014, the global cost of obesity was estimated to be 2 trillion United States dollars (US$), or nearly 3% of the global gross domestic product. Costs include both direct health-care costs

(e.g. treatment of obesity-related conditions) and indirect costs (e.g. productivity losses and premature death) (*4*, *5*). If current trends continue, the global economic costs of obesity and overweight are predicted to exceed US$ 3 trillion by 2030 and reach US$ 18 trillion by 2060 (*6*).

Summary of evidence: benefits

The application presented the results of an unpublished systematic review and network meta-analysis conducted for the purpose of the application. The review updates a previously published systematic review and meta-analysis of pharmacotherapy for adults with overweight and obesity (*7*). The review included 184 randomized controlled trials (80 155 participants) of adults with overweight or obesity, with or without cardiovascular or metabolic comorbidities. It compared weight-lowering pharmacotherapy with lifestyle modification alone or alternative weight-lowering pharmacotherapy. Median treatment duration was 24 weeks, and median length of follow-up was 26 weeks. Important outcomes included: percentage bodyweight change; bodyweight reduction of ≥ 5%, 10%, 15% or 20%; quality-of-life scores; all-cause death; non-fatal myocardial infarction; and non-fatal stroke. There were 78 trials (22 031 participants) involving GLP-1 receptor agonists or GLP-1/GIP dual agonists and these were the only results reported in the application.

All medicines were associated with reductions in bodyweight from baseline compared with lifestyle modification alone: tirzepatide (mean difference (MD) of percentage bodyweight change −15.15, 95% confidence interval (CI) −16.28 to −14.03; eight randomized controlled trials, 3396 participants); semaglutide (oral) (MD −12.70, 95% CI −15.89 to −9.51; one randomized controlled trial, 667 participants); semaglutide (subcutaneous) (MD −9.48, 95% CI −10.24 to −8.72, 18 randomized controlled trials, 24021 participants); liraglutide (MD −4.96%, 95% CI −5.64 to −4.28; 26 one randomized controlled trials, 7756 participants); exenatide (MD −3.58%, 95% CI −4.78 to −2.37; three randomized controlled trials, 320 participants); beinaglutide (MD −3.27, 95% CI −5.67 to −0.87; two randomized controlled trials, 484 participants); and dulaglutide (MD −1.38, 95% CI −3.81 to 1.06; one randomized controlled trial, 91 participants). The certainty of evidence was high for tirzepatide, oral and subcutaneous semaglutide, and moderate for the remaining medicines.

Compared with lifestyle modification alone, beinaglutide, liraglutide, oral and subcutaneous semaglutide and tirzepatide increased the proportions of participants who achieved body weight reduction of at least 5%, 10%, 15% and 20%. The certainty of evidence was very low to high for beinaglutide, high for oral semaglutide, moderate to high for subcutaneous semaglutide, and moderate for liraglutide and tirzepatide. Dulaglutide was not associated with an important increase in the proportion of individuals achieving these outcomes (Table 11).

Table 11
Likelihood of participants achieving weight reduction thresholds with medication compared with lifestyle modification alone

Medicine	Risk ratio (95% CI) Body weight reduction			
	≥ 5%	≥ 10%	≥ 15%	≥ 20%
Beinaglutide	2.29 (1.31 to 4.00)	4.19 (1.61 to 10.91)	6.12 (1.15 to 32.58)	5.39 (0.30 to 96.83)
Dulaglutide	0.71 (0.28 to 1.82)	0.35 (0.13 to 0.91)	0.30 (0.05 to 1.80)	0.43 (0.05 to 3.35)
Exenatide	1.86 (1.18 to 2.93)	2.09 (0.90 to 4.86)	1.38 (0.06 to 31.51)	4.81 (0.14 to 168.82)
Liraglutide	2.28 (1.98 to 2.61)	3.06 (2.47 to 3.78)	3.03 (2.10 to 4.36)	2.50 (1.66 to 3.76)
Semaglutide (oral)	3.53 (2.12 to 5.88)	6.27 (3.21 to 12.23)	9.31 (3.44 to 25.14)	12.45 (6.18 to 25.08)
Semaglutide (subcutaneous)	2.60 (2.28 to 2.95)	5.11 (4.26 to 6.13)	7.72 (5.79 to 10.29)	16.10 (13.10 to 19.79)
Tirzepatide	3.34 (2.78 to 4.03)	6.98 (5.39 to 9.04)	16.69 (11.08 to 25.15)	21.47 (15.21 to 30.31)

For the outcome of all-cause death, there was high-certainty evidence that liraglutide (risk ratio (RR) 0.44, 95% CI 0.08 to 2.25; three randomized controlled trials, 4332 participants), subcutaneous semaglutide (RR 0.81, 95% CI 0.71 to 0.93; six randomized controlled trials, 21 413 participants) and tirzepatide (RR 0.79, 95% CI 0.23 to 2.75; three randomized controlled trials, 2088 participants) reduced the risk of death. There was moderate-certainty evidence that beinaglutide reduced risk of death (RR 0.49, 95% CI 0.01 to 24.58; one randomized controlled trial, 240 participants). In each case, the treatment effect in absolute terms was considered trivial because of the low baseline risk across comparisons.

There was high-certainty evidence that subcutaneous semaglutide reduced the risk of non-fatal myocardial infarction (RR 0.73, 95% CI 0.62 to 0.86; two randomized controlled trials, 17 908 participants). There was moderate-certainty evidence that liraglutide (RR 0.83, 95% CI 0.16 to 4.32; three randomized controlled trials, 4269 participants) and tirzepatide (RR 0.96, 95% CI 0.17 to 5.35; two randomized controlled trials, 652 participants) reduced the risk of non-fatal myocardial infarction. There was high-certainty evidence that subcutaneous

semaglutide reduced the risk of non-fatal stroke (RR 0.93, 95% CI 0.75 to 1.16; one randomized controlled trial, 17 604 participants). In each case, the treatment effects in absolute terms were considered trivial because of the low baseline risk across comparisons and short median follow-up of the trials. Notably, the trials included did not provide sufficient information to stratify populations by risk of cardiovascular or chronic kidney disease. However, the SELECT trial was a multicentre, double-blind randomized, placebo-controlled trial that investigated the effect of semaglutide on cardiovascular outcomes in 17 604 patients with BMI ≥ 27 and preexisting cardiovascular diseases but without diabetes (*8*). The primary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. This trial provided moderate-certainty evidence that semaglutide reduced the risk of all-cause mortality (RR 0.81, 95% CI 0.71 to 0.93; in absolute terms, 10 fewer deaths per 1000 people treated). There was also high-certainty evidence that semaglutide reduced the risk of non-fatal myocardial infarction (RR 0.72, 95% CI 0.61 to 0.85; in absolute terms, 10 fewer events per 1000 people treated). There was moderate-certainty evidence of no significant effect of semaglutide on non-fatal stroke (RR 0.93, 95% CI 0.74 to 1.15).

For the effects of the treatment on quality of life, the review found moderate-certainty evidence that tirzepatide and oral semaglutide were associated with medium improvements in quality-of-life scores, and high-certainty evidence that liraglutide and subcutaneous semaglutide were associated with small improvements in quality-of-life scores.

There was high-certainty evidence that subcutaneous semaglutide and tirzepatide were effective in reducing fat mass with MD from baseline of −18.63% (95% CI −24.21 to −13.05; one randomized controlled trial, 1961 participants) and −25.70% (95% CI −31.53 to −19.87; one randomized controlled trial, 1273 participants), respectively. There was moderate-certainty evidence for liraglutide (MD −7.99%, 95% CI −11.30 to −4.67; three randomized controlled trials, 354 participants) and very-low-certainty evidence for exenatide (MD −4.19, 95% CI −11.07 to 2.69; indirect evidence only) for this outcome. There was high-certainty evidence that subcutaneous semaglutide (MD −7.57%, 95% CI −11.57 to −3.57; one randomized controlled trial, 1961 participants) and tirzepatide (MD −8.30%, 95% CI −12.45 to −4.15; one randomized controlled trial, 1273 participants) were associated with reductions in lean mass from baseline.

Summary of evidence: harms

Results of the systematic review and meta-analysis found that all GLP-1 receptor agonists and GLP-1/GIP dual agonists were associated with increased risk of discontinuation of treatment due to adverse events compared with lifestyle modification alone: beinaglutide RR 5.32, 95% CI 0.87 to 32.41 (two randomized

controlled trials, 484 participants, very-low-certainty evidence); dulaglutide RR 1.02, 95% CI 0.44 to 2.40 (one randomized controlled trial, 91 participants, very-low-certainty evidence); exenatide RR 1.28, 95% CI 0.57 to 2.87 (three randomized controlled trials, 320 participants, low-certainty evidence); liraglutide RR 2.43, 95% CI 1.91 to 3.08 (24 randomized controlled trials, 7604 participants, high-certainty evidence); oral semaglutide RR 1.63, 95% CI 0.72 to 3.70 (one randomized controlled trial, 667 participants, moderate-certainty evidence); subcutaneous semaglutide RR 1.88, 95% CI 1.51 to 2.33 (18 randomized controlled trials, 24 021 participants, high-certainty evidence) and tirzepatide RR 1.91, 95% CI 1.41 to 2.58 (nine randomized controlled trials, 3492 participants, moderate-certainty evidence).

For gastrointestinal events, the most harmful medicines were tirzepatide (RR 3.08, 95% CI 2.49 to 3.81; eight randomized controlled trials, 2913 participants, moderate-certainty evidence), oral semaglutide (RR 2.96, 95% CI 1.65 to 5.32; one randomized controlled trial, 667 participants, high-certainty evidence), liraglutide (RR 2.82, 95% CI 2.45 to 3.25; 25 randomized controlled trials, 7654 participants, moderate-certainty evidence) and subcutaneous semaglutide (RR 2.78, 95% CI 2.35 to 3.29; 14 randomized controlled trials, 5446 participants, moderate-certainty evidence). There was low-certainty evidence of increased risk of gastrointestinal events for beinaglutide, dulaglutide and exenatide compared with lifestyle modification alone.

For the outcome of gall bladder-related disorders, GLP-1 receptor agonists and tirzepatide were no more harmful than lifestyle modification alone. The certainty of evidence was high for subcutaneous semaglutide and tirzepatide, moderate for liraglutide and oral semaglutide and low for dulaglutide. Similarly, for the outcome of fatigue, GLP-1 receptor agonists and tirzepatide were no more harmful than lifestyle modification alone. The certainty of evidence was high for subcutaneous semaglutide, moderate for liraglutide, oral semaglutide and tirzepatide, low for beinaglutide and dulaglutide, and very low for exenatide.

Subcutaneous semaglutide had an RR of 0.78 (95% CI 0.46 to 1.33, high-certainty evidence) for pancreatitis. Liraglutide had an RR of 1.34 (95% CI 0.40 to 4.49, high-certainty evidence) and tirzepatide had an RR of 0.96 (95% CI 0.34 to 2.71, high-certainty evidence). Dulaglutide had an RR of 0.32 (95% CI 0.01 to 9.25, moderate-certainty evidence).

In the SELECT trial of semaglutide in obesity without diabetes (*8*), serious adverse events were reported more frequently in the placebo group than the semaglutide group. Adverse events (any grade) leading to treatment discontinuation occurred more frequently in the semaglutide group than the placebo group (16.6% versus 8.2%). The most frequently reported adverse events leading to treatment discontinuation were gastrointestinal disorders.

Additional evidence

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WHO guidelines

As of May 2025, WHO guidelines on the use of and indications for GLP-1 RA and GLP-1 /GIP dual agonists in the treatment of adults with obesity were being developed.

WHO convened the guideline development group on 7–9 April 2025, to be able to inform the Expert Committee. This group made a conditional recommendation for the use of GLP-1 and GLP-1/GIP dual agonists in the treatment of adults with obesity. The critical outcomes that informed this decision were weight, quality of life, adverse events, major adverse cardiovascular events and mortality.

Publication of the guidelines is expected in the fourth quarter of 2025.

Costs/cost–effectiveness

The application identified two systematic reviews that evaluated the cost–effectiveness of liraglutide, semaglutide and other weight-loss interventions for obesity management in adults and adolescents (*9*, *10*). Additionally, the application includes a summary of the United Kingdom's National Institute for Health and Care Excellence technology appraisal of tirzepatide (*11*).

One review found that semaglutide offered more quality-adjusted life years and was associated with more costs compared with phentermine plus topiramate, phentermine monotherapy, and naltrexone plus bupropion. Incremental cost–effectiveness ratios exceeded willingness-to-pay thresholds. Semaglutide appeared to be cost-effective compared with diet and exercise and liraglutide, but was not cost-effective compared with surgical interventions (sleeve gastrectomy, endoscopic sleeve gastroplasty and gastric bypass). The total cost of semaglutide in patients with class III obesity (BMI ≥ 40 kg/m^2) was reported as 409 571 United States dollars (US$), while costs for endoscopic sleeve gastroplasty and sleeve gastrectomy were US$ 183 355 and US$ 188 844 respectively (*9*).

A 2024 economic analysis found that semaglutide would need to have a three-fold reduction in its annual cost to not be dominated by endoscopic sleeve gastroplasty for patients with stage II obesity (BMI 35–39.9 kg/m^2) (*12*).

A 2025 Canadian study evaluated the cost–effectiveness of semaglutide in overweight or obese patients with pre-existing cardiovascular disease and without diabetes (*13*). In the base case, semaglutide had an incremental cost–effectiveness ratio of 72 962 Canadian dollars (Can$) per quality-adjusted life year (QALY) gained compared with standard care. There was a 14% probability of semaglutide being cost-effective at a willingness-to-pay threshold of Can$ 50 000.

The incremental cost–effectiveness ratio was sensitive to the mortality benefit and medication cost. With a 50% price reduction, the resultant incremental cost–effectiveness ratio was Can$ 37 724 per QALY gained, for which there was a 75% probability of being cost-effective at a willingness-to-pay threshold of Can$ 50 000.

The NICE appraisal found tirzepatide to have an acceptable incremental cost–effectiveness ratio as an option for managing overweight and obesity in adults, along with a reduced calorie diet and increased physical activity, only in the subgroup of patients with an initial BMI of ≥ 35 kg/m^2 and at least one weight-related comorbidity (*11*).

A 2023 modelling study evaluated the cost–effectiveness of liraglutide, semaglutide, tirzepatide, naltrexone plus bupropion, and phentermine plus topiramate as treatments for obesity from a United States payer perspective (*14*). Over a lifetime horizon, all treatments had similar QALYs although it was slightly greater for tirzepatide. The medicines differed in cost from US$ 118 900 for phentermine plus topiramate to US$ 308 767 for semaglutide. The lifetime cost for tirzepatide was US$ 234 084. The incremental cost–effectiveness ratio for tirzepatide relative to phentermine plus topiramate was US$ 355 616 per QALY, exceeding the willingness-to-pay threshold of US$ 150 000 per QALY. Sensitivity analyses indicated that the price of tirzepatide would need to be reduced by almost 40% to be cost-effective at this willingness-to-pay threshold.

The application noted potential limitations of the cost–effectiveness studies including: short follow-up periods that limit insight into the sustainability of weight loss; predominance of studies in high-income countries, with limited representation of low- and middle-income settings; effect of high cost and adverse events on adherence and real-world outcomes; and underreporting of non-monetary benefits such as improved productivity and quality of life in the economic evaluations.

The application reported monthly prices of semaglutide and tirzepatide in different countries ranging from US$ 83 in France to US$ 936 in the United States of America for semaglutide, and from US$ 150 in the United Kingdom of Great Britain and Northern Ireland to US$ 1023 in the United States for tirzepatide.

Availability

Subcutaneous semaglutide has regulatory and marketing approval for use in the treatment of obesity in many high-income countries, but regulatory approval and market availability in low- and middle-income countries is more limited and variable. Basic patent expiry is reported for March 2026. Biosimilars are not currently available, although they are in development in some countries (e.g. India).

Liraglutide has regulatory and marketing approval for use in the treatment of obesity in many countries globally. Key patents are expected to expire in 2026.

Some companies are already marketing biosimilar liraglutide in China, India and the United Kingdom (*15*).

Tirzepatide has regulatory and marketing approval for use in the treatment of obesity in several high-income countries. Its availability is expected to expand globally as regulatory applications are approved in other settings. It remains under patent protection until at least 2030 and biosimilar competition is unlikely in the near future.

Information on the availability of other GLP-1 receptor agonists was not provided in the application.

Other considerations

The Expert Committee considered two separate applications for GLP-1 receptor agonists: one for the treatment of adults with type 2 diabetes and established or at high-risk of cardiovascular disease, and one for the treatment of adults with obesity.

While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms across the two conditions and to understand the implications of coverage for the two cohorts of patients at global, regional and national levels. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

Committee recommendations

The Expert Committee recognized that diabetes and obesity currently represent two major global health challenges, with both conditions reaching epidemic proportions in different populations and regions. According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes. At the same time, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affecting more than 1 billion people. Growth in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are major contributors to mortality and morbidity, are responsible for substantial disability-adjusted life years and strain health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and

obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with either diabetes or obesity alone.

The Committee noted the evidence from the large systematic review that demonstrated the efficacy of glucagon-like-peptide-1 (GLP-1) receptor agonists (particularly subcutaneous semaglutide, for which more data have been cumulated) and tirzepatide in people with obesity for achieving clinically meaningful weight loss and improving quality of life, compared with lifestyle modification alone. However, the Committee agreed that evidence of benefits in cardiovascular outcomes and mortality in people with obesity without diabetes was currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events in people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence on mortality outcomes was still at an early stage and limited.

The Committee noted the evidence from multiple large-scale randomized controlled trials and systematic reviews that demonstrated the efficacy of GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide in people with diabetes in improving glycaemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), reducing the risk of end-stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss, compared with placebo. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit was possible in all patients irrespective of risk of cardiovascular diseases, patients with type 2 diabetes with known cardiovascular or chronic kidney disease are a high-risk subgroup that is likely to experience the most relevant benefit, with a 10-fold decreased risk of premature death compared with the cohort of patients at low risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify those patients to be prioritized in the introduction of these medicines at the country level.

Overall, the Committee considered that the magnitude of benefits and certainty of evidence for GLP-1 receptor agonists and tirzepatide were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee places greater value than outcomes of glycaemic control and weight loss.

The Expert Committee therefore did not recommend the inclusion of GLP-1 receptor agonists and tirzepatide on the EML for the treatment of people with obesity without type 2 diabetes and established cardiovascular disease or

chronic kidney disease, because of less relevant and mature evidence of benefit for cardiovascular outcomes and mortality in this population, and a lack of data about long-term net benefit to harm balance.

However, in consideration of the application for GLP-1 receptor agonists for the treatment of adults with type 2 diabetes and established or at high-risk of cardiovascular disease, the Expert Committee recommended the inclusion of semaglutide, dulaglutide, liraglutide and tirzepatide on the core list of the EML as add-on glucose-lowering therapy for adults with type 2 diabetes and with (i) established cardiovascular disease or chronic kidney disease; and (ii) obesity (BMI $\geq 30\,kg/m^2$) having a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Refer to the summary for the addition of GLP-1 receptor agonists for use in adults with type 2 diabetes for full details of the Expert Committee's recommendation for this indication.

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Glucagon-like peptide-1 receptor agonists – addition diabetes – EML

Semaglutide — ATC code: A10BJ06

Proposal

Addition of semaglutide to the core list of the EML for the treatment of adults with type 2 diabetes mellitus and established or at high-risk of cardiovascular disease. Listing is proposed with a square box as the representative glucagon-like-peptide-1 (GLP-1) receptor agonist, with dulaglutide and liraglutide as therapeutic alternatives.

Applicant

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WHO technical department

The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical department supported the inclusion of GLP 1 receptor agonists on the EML as an option for add-on glucose-lowering therapy when sodium glucose cotransporter-2 inhibitors are not tolerated, cause side-effects or are ineffective.

EML/EMLc

EML

Section

18.5.2 Hypoglycaemic agents

Dose form(s) & strengths(s)

Injection solution: 0.68 mg/mL, 0.34 mg/mL, 2.68 mg/mL

Core/complementary

Core

Individual/square box listing

Square box, with dulaglutide and liraglutide as the specified therapeutic alternatives.

Other GLP-1 receptor agonists exist (e.g. albiglutide, exenatide, lixisenatide); however, these were not reviewed in the application or proposed for inclusion in the EML due to lack of proven cardiovascular benefit (exenatide, lixisenatide) and market withdrawal (albiglutide).

Background

In 2017, the Expert Committee considered a review of medicines for second-line therapy for type 2 diabetes, including (but not limited to) GLP1 receptor agonists and sodium–glucose cotransporter-2 (SGLT2) inhibitors, based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health. The Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (*1*).

In 2021, the Expert Committee reviewed an application presenting new evidence which confirmed the positive effect of SGLT2 inhibitors compared with placebo on: all-cause mortality; cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina); renal outcomes (kidney failure end-stage renal disease and renal death); body weight; and glycated haemoglobin (HbA1c). The Committee noted that the situation was less clear when comparing SGLT2 inhibitors with GLP-1 receptor agonists, although the SGLT2 inhibitors seemed to be the preferred option as they were consistently associated with favourable results for most cardiovascular outcomes and were administered orally in contrast to GLP-1 receptor agonists that needed to be injected. For SGLT2 inhibitors, the Committee considered that there was high-quality evidence showing clinically beneficial effects in patients with type 2 diabetes who had not achieved appropriate glycaemic control with metformin or a sulfonylurea, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy. Additionally, there was a reasonable safety profile. The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy. GLP-1 receptor agonists were not recommended for inclusion for second-line therapy for type 2 diabetes at that time (*2*).

In 2023, the Expert Committee considered an application for inclusion of GLP-1 receptor agonists on the EML for the treatment of obesity. The Expert committee did not recommend GLP-1 receptor agonists for weight loss in obesity because of uncertain long-term clinical benefit and safety in this population. The Committee noted the wide use of these medicines in the treatment of type 2 diabetes and advice from the applicant of a planned submission in 2025 for consideration of GLP-1 receptor agonists for use in the treatment of type 2 diabetes (*3*).

Public health relevance

According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes.(4). The prevalence is increasing over time and is accompanied by a substantial rise in associated complications, including cardiovascular disease, which remains a leading cause of morbidity and mortality in people with diabetes. Based on previous studies, the weighted prevalence for established or high-risk cardiovascular disease is around 30% in adults with type 2 diabetes (5, 6).

In 2021, diabetes was responsible for 1.6 million deaths and 47% of all deaths due to diabetes occurred in people younger than 70 years. Another 530 000 kidney disease deaths were caused by diabetes, and high blood glucose causes around 11% of cardiovascular deaths (7).

Summary of evidence: benefits

The application presented brief summaries of randomized trials and systematic reviews of semaglutide and other GLP-1 receptor agonists investigating the effects of the treatments on cardiovascular outcomes and diabetes outcomes. The following summary has been elaborated by the EML Secretariat.

Semaglutide

The SUSTAIN 6 trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of semaglutide in 3297 participants with type 2 diabetes on a standard-care regimen (8). Participants were randomly assigned to receive weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. At baseline, 83% of participants had established cardiovascular disease, chronic kidney disease or both. The primary outcome was the first occurrence of major adverse cardiovascular events (MACE): a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The primary outcome occurred in 108/1648 (6.6%) and 146/1649 (8.9%) of participants in the semaglutide and placebo groups, respectively (hazard ratio (HR), 0.74, 95% confidence interval (CI) 0.58 to 0.95; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority). Semaglutide was associated with a significant reduction in the risk of non-fatal stroke (HR 0.61, 95% CI 0.38 to 0.99). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.74, 95% CI 0.51 to 1.08), cardiovascular death (HR 0.98, 95% CI 0.65 to 1.48) or all-cause mortality (HR 1.05, 95% CI 0.74 to 1.50). Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (HR 1.76, 95% CI 1.11 to 2.78; $P = 0.02$). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment due to

adverse events, mainly gastrointestinal. The study concluded that in patients with type 2 diabetes at high cardiovascular risk, semaglutide significantly reduced the rate of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared with placebo, confirming the non-inferiority of semaglutide

A manufacturer-sponsored post hoc analysis assessed the consistency of the cardiovascular effect of semaglutide across subgroups at different baseline cardiovascular risk levels in the SUSTAIN 6 trial (*9*). Subgroup analyses were performed for patients with or without a history of prior myocardial infarction or stroke, and patients with cardiovascular risk factors or established cardiovascular disease. Point estimates for the HRs were all below 1.0, favouring semaglutide; however, no significant differences were found between treatment groups for each subgroup.

The SELECT trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated cardiovascular outcomes of semaglutide in 17 604 participants with obesity and atherosclerotic cardiovascular disease, and a history of heart failure (*10*). Participants were randomized to receive escalating doses of once-weekly semaglutide over 16 weeks to a target dose of 2.4 mg or placebo. The primary outcomes in the prespecified analysis were time from randomization to first occurrence of: MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); a composite heart failure outcome (cardiovascular death or hospitalization or urgent hospital visit for heart failure); cardiovascular death; and all-cause death. The study also examined the effects of semaglutide in patients with heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Semaglutide was associated with improvements in all outcome measures in patients with heart failure compared with those without heart failure. The HRs for MACE, the composite heart failure endpoint, cardiovascular death and all-cause death were 0.72 (95% CI0.60 to 0.87), 0.79 (95% CI 0.64 to 0.98), 0.76 (95% CI 0.59 to 0.97) and 0.81 (95% CI 0.66 to 1.00), respectively. In participants with heart failure, semaglutide was also associated with improved outcomes for MACE in both heart failure with preserved ejection fraction (HR 0.69, 95% CI 0.51 to 0.91) and heart failure with reduced ejection fraction (HR 0.65, 95% CI 0.49 to 0.87) groups.

Liraglutide

The LEADER trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of liraglutide in 9340 participants with type 2 diabetes and high cardiovascular risk (*11*). Participants were randomized to receive liraglutide (1.8 mg or maximum tolerated dose daily) or placebo, with a median follow-up of 3.8 years. The primary outcome was the first occurrence of MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The primary outcome occurred

in 608/4668 (13.0%) and 694/4672 (14.9%) of participants in the liraglutide and placebo groups, respectively (HR 0.87, 95% CI 0.78 to 0.97; $P < 0.001$ for non-inferiority; $P = 0.01$ for superiority). Liraglutide was associated with a significantly lower risk of death from cardiovascular causes (HR 0.78, 95% CI 0.66 to 0.93) and death from any cause (HR 0.85, 95% CI 0.74 to 0.97). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.88, 95% CI 0.75 to 1.03) or non-fatal stroke (HR 0.89, 95% CI 0.72 to 1.11).

A randomized, parallel-group trial compared the effectiveness of liraglutide, insulin glargine, glimepiride (a sulfonylurea) and sitagliptin (a dipeptidyl peptidase-4 inhibitor) in maintaining target HbA1c levels in 5047 participants with type 2 diabetes receiving metformin (*12*). The primary outcome was primary metabolic failure of the assigned treatment, defined as HbA1c of 7% or higher at quarterly measurements. Over a mean follow-up of 5 years, 71% of participants experienced primary metabolic failure events, including 860/1262 (68.2%) participants receiving liraglutide, 852/1263 (67.4%) participants receiving insulin glargine, 908/1254 (72.4%) participants receiving glimepiride and 981/1268 (77.4%) participants receiving sitagliptin. In pairwise comparisons, both liraglutide and insulin glargine were associated with a significantly lower risk of primary metabolic failure compared with glimepiride and sitagliptin. No significant difference was seen between liraglutide and insulin glargine.

Dulaglutide

The REWIND trial was a manufacturer-sponsored randomized, double-blind, placebo-controlled trial that evaluated the cardiovascular outcomes of dulaglutide in 9901 participants with type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors (*13*). Participants were randomized to receive dulaglutide 1.5 mg weekly or placebo, with a median follow-up of 5.4 years. The primary outcome was the first occurrence of MACE (a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke). The primary outcome occurred in 594/4949 (12.0%) and 663/4952 (13.4%) of participants in the dulaglutide and placebo groups, respectively (HR 0.88, 95% CI 0.79 to 0.99; $P = 0.02$ for superiority). Dulaglutide was associated with a significant reduction in the risk of non-fatal stroke (HR 0.76, 95% CI 0.61 to 0.95). No significant differences were seen between treatment groups for non-fatal myocardial infarction (HR 0.96, 95% CI 0.79 to 1.16), cardiovascular death (HR 0.91, 95% CI 0.78 to 1.6) or all-cause mortality (HR 0.90, 95% CI 0.80 to 1.01).

Systematic reviews

A 2023 systematic review and network meta-analysis of 816 randomized controlled trials (471 038 participants) compared the benefits and harms of various pharmacological treatments for adults with type 2 diabetes (*14*). Primary

outcomes included all-cause death, cardiovascular death, non-fatal myocardial infarction, admission to hospital for heart failure and end-stage kidney disease. The analysis found high-certainty evidence that relative to standard treatments, GLP-1 receptor agonists reduced all-cause death (odds ratio (OR) 0.88, 95% CI 0.82 to 0.93) and cardiovascular death (OR 0.87, 95% CI% 0.81 to 0.94). Similar results were also found for SGLT-2 inhibitors. There was moderate-certainty evidence that GLP-1 receptor agonist reduced the risk of non-fatal myocardial infarction (OR 0.91, 95% CI 0.85 to 0.98), while there was high-certainty evidence for SGLT-2 inhibitors for this outcome (OR 0.90, 95% CI 0.82 to 0.98). There was high-certainty evidence that GLP-1 receptor agonists reduced the risk of non-fatal stroke (OR 0.85, 95% CI 0.77 to 0.94). There was also moderate-certainty evidence that GLP-1 receptor agonists decreased hospital admissions for heart failure (OR 0.91, 95% CI 0.83 to 0.99) and reduced end-stage kidney disease (OR 0.83, 95% CI 0.75 to 0.92)

A 2021 systematic review and meta-analysis of eight randomized controlled trials (60 080 participants) evaluated cardiovascular, mortality and renal outcomes associated with GLP-1 receptor agonists in adults with type 2 diabetes (*15*). The analysis found that GLP-1 receptor agonists significantly reduced MACE (HR 0.86, 95% CI 0.80 to 0.93), all-cause mortality (HR 0.88, 95% CI 0.82 to 0.94), hospital admission for heart failure (HR 0.89, 95% CI 0.82 to 0.98) and a composite kidney outcome (defined as development of macroalbuminuria, doubling of serum creatinine or at least a 40% decline in estimated glomerular filtration rate, kidney replacement therapy, or death due to kidney disease; worsening of kidney function, based on estimated glomerular filtration rate change) (HR 0.79, 95% CI 0.73 to 0.87).

A 2020 systematic review and network meta-analysis of 453 randomized trials (320 474 participants) evaluated the comparative effectiveness and safety of 21 glucose-lowering medicines from nine pharmacological classes in adults with type 2 diabetes (*16*). Most of the studies were industry funded: 134 (41 862 participants) evaluated monotherapy, 296 (264 087) evaluated add-on therapy to metformin and 23 (14 525 participants) evaluated both monotherapy and add-on therapy. Compared with placebo, all treatments were associated with significant reductions in HbA1c. In treatment-naïve patients, subcutaneous semaglutide, liraglutide and dulaglutide were associated with mean differences (MD) of −1.48% (95% CI −2.15% to −0.81%), −1.45% (95% CI −2.18% to −0.72%) and −1.29% (95% CI −1.96% to −0.62%), respectively. Confidence in the estimates was moderate for subcutaneous semaglutide and low for liraglutide and dulaglutide. Among patients receiving metformin-based therapy, MD in HbA1c for subcutaneous semaglutide, liraglutide and dulaglutide were −1.33% (95% CI −1.50% to −1.16%), −0.80% (95% CI −0.89% to −0.70%) and −0.89% (95% CI −1.05% to −0.73%), respectively. Confidence in the estimates was high for the three GLP-1 receptor

agonists. For patients at increased cardiovascular risk receiving metformin-based therapy, the meta-analysis found that liraglutide significantly reduced the risk of cardiovascular death compared with placebo (OR 0.78, 95% CI 0.65 to 0.93, moderate confidence in estimate; however, no significant differences were reported for subcutaneous semaglutide or dulaglutide. Additionally, no significant differences were found between subcutaneous semaglutide, liraglutide dulaglutide and placebo for hospitalizations due to heart failure.

A 2019 manufacturer-sponsored review presented an overview of the results of the efficacy trials of semaglutide versus placebo (SUSTAIN 1, 5 and 6), sitagliptin (SUSTAIN 2), extended-release exenatide (SUSTAIN 3), insulin glargine (SUSTAIN 4) and dulaglutide (SUSTAIN 7) (*17*). The trials included patients with type 2 diabetes who were inadequately controlled on standard treatments and measured changes from baseline to end of treatment in HbA1c as the primary efficacy endpoint. Across the trials, mean HbA1c decreased significantly from baseline by 1.2–1.5% with semaglutide 0.5 mg and 1.5–1.8% with semaglutide 1.0 mg, compared with <0.1–0.4% with placebo and 0.5–1.4% with full doses of active comparators. The trials also reported greater reductions in body weight associated with semaglutide compared with placebo and active comparators. Mean body weight reductions were 3.5–4.6 kg with semaglutide 0.5 mg, 4.5–6.5 kg with semaglutide 1.0 mg, 1.0–1.4 kg with placebo, 3.0 kg with dulaglutide and 1.9 kg with sitagliptin and exenatide.

A 2018 meta-analysis of the LEADER, SUSTAIN 6 and EXSCEL (exenatide once weekly) trials investigated the overall effect of GLP-1 receptor agonists on MACE and included subgroup analyses in order to identify subpopulations that may show the greatest cardiovascular benefit (*18*). The meta-analysis found that compared to placebo, GLP-1 receptor agonists were associated with significant risk reductions in MACE (relative risk (RR) 0.88, 95% CI 0.81 to 0.97) and cardiovascular death (RR 0.85, 95% CI 0.75 to 0.95). Reduction in risk of non-fatal myocardial infarction and non-fatal stroke were not significantly different. Subgroup analyses found no significant difference between GLP-1 receptor agonists and placebo for all subgroups with the exception of race, compared with parameters within the same subgroup category. Within the subgroup of race, there were trends towards a reduced risk of MACE in participants of African (RR 0.78, 95% CI 0.60 to 0.99) and Asian (RR 0.35, 95% CI 0.09 to 1.32) origin. A post hoc analysis found that only Asians participants had a significant reduction in risk of MACE from treatment compared with white participants.

A 2018 systematic review and meta-analysis of 12 randomized controlled trials (9501 participants) assessed the efficacy and safety of semaglutide (subcutaneous or oral) versus placebo or active comparators in adults with type 2 diabetes (*19*). The primary outcome was change from baseline in HbA1c. For subcutaneous semaglutide versus placebo, significant differences were seen

in change in HbA1c favouring semaglutide 0.5 mg (weighted mean difference (WMD) −1.01% (95% CI −1.47% to −0.56%) and semaglutide 1 mg (WMD −1.38%, 95% CI −1.70% to −1.05%). Compared with active comparators, significant differences were also seen favouring semaglutide 0.5 mg (WMD −0.63%, 95% CI −0.95% to −0.31%) and semaglutide 1 mg (WMD −0.84%, 95% CI −1.23% to −0.44%). Compared with placebo, significant differences were observed in change in body weight favouring semaglutide 0.5 mg (WMD −2.32 kg, 95% CI −3.19 kg to −1.46 kg) and semaglutide 1 mg (WMD −4.11 kg, 95% CI −4.85 kg to −3.37 kg). Similarly, compared with active comparators, semaglutide was associated with significant differences in change in body weight (WMD −2.28 kg, 95% CI −3.42 kg to −1.14 kg for 0.5 mg semaglutide and WMD −3.78 kg, 95% CI −4.90 kg to −2.66 kg for 1 mg semaglutide).

A 2018 manufacturer-sponsored systematic review and network meta-analysis of 26 studies (number of participants not reported) compared the efficacy and safety of once-weekly semaglutide 0.5 mg and 1 mg with other GLP-1 receptor agonists in patients with type 2 diabetes who were inadequately controlled on 1–2 oral antidiabetic medicines (*20*). Semaglutide 1 mg was associated with significantly greater reductions in HbA1c and weight and greater odds of achieving HbA1c levels of < 7% or ≤ 6.5% compared with all other GLP-1 receptor agonists. Semaglutide 0.5 mg was associated with similar outcomes compared with most comparators. No significant differences were seen between either dose of semaglutide and other GLP-1 receptor agonists for discontinuations due to adverse effects.

Summary of evidence: harms

Gastrointestinal side-effects are among the most reported adverse events associated with GLP-1 receptor agonists. These include nausea, vomiting, diarrhoea and constipation (*12*, *14*, *19*, *21*). In the SUSTAIN trials, the incidence of nausea was significantly higher in the semaglutide groups compared with placebo (*8*, *17*).

Pancreatitis is a serious but relatively rare adverse event associated with GLP-1 receptor agonists (*19*). Clinical trials and post-marketing surveillance have reported cases of acute pancreatitis in patients treated with these agents. Participants with a history of pancreatitis were largely excluded from the main clinical trials.

The use of GLP-1 receptor agonists has been associated with an increased risk of diabetic retinopathy (*19*). A 2021 meta-analysis and meta-regression examined the associations between retinopathy, HbA1c, systolic blood pressure and weight in six GLP-1 receptor agonist cardiovascular outcome trials (*22*). The meta-analysis showed no association between GLP-1 receptor agonist treatment and retinopathy (OR 1.10, 95% CI 0.93 to 1.30). Univariate meta-regression

showed an association between retinopathy and average HbA1c reduction during the overall follow-up. A 0.1% increase in HbA1c reduction was associated with increased log OR for retinopathy at 3 months, 1 year and overall. The study concluded that HbA1c reduction was significantly associated with increased retinopathy risk in the meta-regression of cardiovascular outcome trials of GLP-1 receptor agonists. The magnitude of HbA1c reduction was correlated with retinopathy risk, but the long-term effect of improved glycaemic control on retinopathy was not measured.

The SUSTAIN 6 trial reported a higher incidence of diabetic retinopathy complications in the semaglutide group compared with the placebo group (HR 1.76, 95% CI 1.11 to 2.78) (*8*). Increased risk of diabetic retinopathy has also been reported in other studies (*16*).

The risk of hypoglycaemia with GLP-1 receptor agonists is generally low when these agents are used as monotherapy or in combination with non-insulin antidiabetic medicines (*23*). Risk increases when GLP-1 receptor agonists are used in combination with insulin or sulfonylureas.

Additional evidence

Evidence for tirzepatide

The SURPASS-1 trial was a 40-week, double-blind, randomized phase III trial that evaluated the efficacy, safety and tolerability of tirzepatide monotherapy versus placebo in adults with type 2 diabetes inadequately controlled by diet and exercise (*24*). A total of 478 participants were randomized 1:1:1:1 to receive tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. The primary efficacy endpoint was mean change in glycated haemoglobin (HbA1c) from baseline to 40 weeks. Each tirzepatide dose was superior to placebo for the primary endpoint, as well as for fasting serum glucose, bodyweight and HbA1c targets of less than 7.0% and 5.9%. For the three doses of tirzepatide, the least-squares mean changes from baseline in HbA1c were −1.87%, −1.89% and −2.07%, respectively. Mean changes in bodyweight from baseline to 40 weeks were −7.0 kg, −7.8 kg and −9.5 kg for tirzepatide 5 mg, 10 mg and 15 mg, respectively. The most frequently reported treatment-emergent adverse events with tirzepatide were gastrointestinal adverse events. Discontinuations due to gastrointestinal adverse events occurred more frequently in participants receiving tirzepatide. The proportion of participants experiencing serious adverse events was similar between treatment groups.

The SURPASS-2 trial was a 40-week, open-label, randomized phase III trial that compared efficacy and safety of tirzepatide with semaglutide in adults with type 2 diabetes (*25*). A total of 1879 participants were randomized 1:1:1:1: to receive tirzepatide 5 mg, 10 mg or 15 mg once weekly or semaglutide 1 mg once weekly. The primary endpoint was change from baseline to week 40 in glycated HbA1c. Secondary endpoints included change from baseline to week 40 in

body weight and in the glycated haemoglobin level from baseline to week 40. Secondary endpoints were change in body weight from baseline to week 40 and HbA1c targets of less than 7.0% and 5.9%. For the primary endpoint, all doses of tirzepatide were superior to semaglutide with estimated treatment differences of −0.15 percentage points (95% CI −0.28 to −0.03) with 5 mg; −0.39 percentage points (95% CI −0.51 to −0.26) with 10 mg; and −0.45 percentage points (95% CI −0.57 to −0.32) with 15 mg. Similarly, for the outcome of change in bodyweight, all doses of tirzepatide were superior to semaglutide. Weight reduction with tirzepatide was dose-dependent with increasing doses associated with greater reductions. The proportions of participants who achieved HbA1c targets were greater in participants receiving tirzepatide.

A 2022 meta-analysis of seven randomized controlled trials (7215 participants) of at least 26 weeks duration from the SURPASS clinical development programme for tirzepatide for type 2 diabetes evaluated risk of cardiovascular event with tirzepatide ($n = 4887$) compared with a pooled comparator group comprising placebo ($n = 286$), insulin degludec ($n = 360$), insulin glargine ($n = 1000$), semaglutide ($n = 469$) and dulaglutide ($n = 213$) (*26*). The primary objective was to compare the time to first occurrence of confirmed four-component major adverse cardiovascular events (MACE-4, i.e. cardiovascular death, myocardial infarction, stroke or hospitalized unstable angina) between tirzepatide and pooled comparator groups. Tirzepatide was associated with numerically lower but statistically non-significant risks of MACE-4 (HR 0.80, 95% CI 0.57 to 1.11), cardiovascular death (HR 0.90, 95% CI 0.50 to 1.61), myocardial infarction (HR0.76, 95% CI 0.45 to 1.28), stroke (HR 0.81, 95% CI 0.39 to 1.68) and hospitalization for unstable angina (HR 0.43, 95%–CI 0.15 to 1.41).

A 2024 retrospective cohort study evaluated the effects of tirzepatide compared with GLP-1 receptor agonists on all-cause mortality and secondary outcomes including MACE, a composite of MACE and all-cause mortality, kidney events, acute kidney injury, and major adverse kidney events in 104 308 adults with type 2 diabetes in the United States of America (*27*). About 10% of participants received tirzepatide. Tirzepatide was associated with significantly lower risk of all outcomes investigated compared with GLP-1 receptor agonist: all-cause mortality (adjusted HR 0.58, 95% CI 0.45 to 0.75); MACE (adjusted HR 0.80, 95% CI 0.71 to 0.91); composite of MACE and all-cause mortality (adjusted HR 0.76, 95% CI 0.68 to 0.84); kidney events (adjusted HR 0.52, 95% CI 0.37 to 0.73); acute kidney injury (adjusted HR 0.78, 95% CI 0.70 to 0.88); and major adverse kidney events (adjusted HR 0.54, 95% CI 0.44 to 0.67).

The SUMMIT trial was a 52-week, double-blind, randomized phase III trial that evaluated the effects of tirzepatide on cardiovascular outcomes in 731 adults with heart failure with preserved ejection fraction and obesity (*28*). Participants were randomized 1:1 to receive tirzepatide up to 15 mg weekly or placebo. Almost

half of the participants in each treatment group had type 2 diabetes. Primary endpoints were a composite of death from cardiovascular causes of a worsening heart failure event and change in Kansas City Cardiomyopathy Questionnaire clinical summary score from baseline to 52 weeks. Treatment with tirzepatide was associated with a reduced risk of cardiovascular death or worsening heart failure compared with placebo (9.9% versus 15.3%; HR 0.62, 95% CI 0.41 to 0.95). After 52 weeks, mean change (standard deviation) in clinical summary score was greater in the tirzepatide group (19.5 (1.2)) than the placebo group (12.7 (1.3)); between-group difference was 6.9 (95% CI 3.3 to 10.6).

WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus did not consider GLP-1 receptor agonists as the guidelines excluded non-insulin injectable antidiabetic medicines (*29*).

Various national and international guidelines currently include recommendations for the use of GLP-1 receptor agonists in patients with type 2 diabetes, as listed in the application.

Costs/cost–effectiveness

The application reported lowest available costs per day of treatment from a 2023 analysis of public databases for the proposed medicines in selected countries (Table 12).

Table 12
Lowest available cost of glucagon-like-peptide-1 receptor agonists

Country	Cost, US$/day		
	Dulaglutide	Liraglutide	Semaglutide
Bangladesh	3.49	5.75	1.27
Brazil	1.91	2.62	3.17
El Salvador	5.01	11.07	Not reported
France	0.74	3.79	4.54
India	2.77	4.63	Not reported
Latvia	Not reported	4.75	7.63
Philippines	2.94	4.66	Not reported

Table 12 *continued*

Country	Cost, US$/day		
	Dulaglutide	Liraglutide	Semaglutide
South Africa	2.85	3.95	3.84
United Kingdom of Great Britain and Northern Ireland	0.79	3.95	2.42
United States of America	7.58	28.38	11.73

US$: United States dollars.

A 2024 report by the Médecins Sans Frontières Access Campaign compared the range of lowest monthly prices of diabetes medicines, including GLP-1 receptor agonists, in 12 countries with their estimated cost-based prices. The analysis estimated that injectable semaglutide could be sold with a profit for US$ 0.89/month, compared to the current global prices being charged of 95–353 United States dollars (US$) per month (*30*). Biosimilar manufacturing could introduce market competition and lead to substantial price reductions.

A 2021 study estimated price targets for incremental costs of switching to newer treatments to achieve cost–effectiveness in low- and middle-income countries (*31*). The analysis included use of these agents as add-on therapies in a so-called glycaemia-agnostic setting for people with cardiovascular disease, heart failure or chronic kidney disease. The study determined that the cost–effectiveness ratios for SGLT2 inhibitors and GLP-1 receptor agonists could be substantially reduced (by 92% for SGLT2 inhibitors and by 72% for GLP-1 receptor agonists) by targeting treatment to patients with type 2 diabetes with these comorbidities.

A 2022 cost–effectiveness study evaluated the lifetime cost–effectiveness of first-line treatment with SGLT2 inhibitors or GLP-1 inhibitors from the United States health-care sector perspective (*32*). In the base-case analysis, SGLT2 inhibitors were associated with higher costs and more quality-adjusted life years (QALY) compared with metformin, with an incremental cost–effectiveness ratio of US$ 478 000 per QALY gained, while GLP-1 receptor agonists had higher costs and reduced QALYs (i.e. were dominated). In a sensitivity analysis when injection disutility was removed, the incremental cost–effectiveness ratio for GLP-1 receptor agonists was US$ 327 000 per QALY gained. Of note, this study was not designed to evaluate the cost–effectiveness specifically in the subgroup of patients with type 2 diabetes and established or at high risk for cardiovascular disease.

A 2024 systematic review evaluated nine cost–effectiveness studies of newer pharmacological treatments for type 2 diabetes (*33*). The studies were non-industry-funded cost-effectiveness analyses from a United States perspective.

Three studies estimated the cost–effectiveness of using GLP-1 receptor agonists as second-line therapy versus various comparators. The review found moderate-certainty evidence that addition of daily oral or weekly injectable GLP-1 receptor agonist was probably of intermediate value with the incremental cost–effectiveness ratios ranging from US$ 50 000 to US$ 150 000 per QALY gained compared with continuing metformin alone. Two studies estimated the cost–effectiveness in the third-line setting (added to metformin and sulfonylureas). The incremental cost–effectiveness ratios were US$ 122 000 and > US$ 150 000 per QALY gained for the addition of a GLP-1 receptor agonist compared with adding no additional treatment or neutral protamine Hagedorn insulin, a dipeptidyl peptidase 4 inhibitor or an SGLT2, respectively.

The application stated that due to recent and upcoming patent expirations for GLP-1 receptor agonists, there will be opportunities for multisource manufacturing and meaningful price reductions.

Availability

Semaglutide injection has regulatory and marketing approval in many high-income countries, but regulatory approval and market availability in low- and middle-income countries is more limited and variable. Basic patent expiry is reported for March 2026. Biosimilars are not currently available, although are in development in some countries (e.g. India).

Liraglutide has regulatory and marketing approval in many countries globally. Some companies are already marketing biosimilar liraglutide in China, India and the United Kingdom (*34*).

No information was presented in the submission on the availability of dulaglutide.

Other considerations

The Expert Committee considered two separate applications involving GLP-1 receptor agonists: one for the treatment of adults with type 2 diabetes and established or at high risk of cardiovascular disease and one for the treatment of adults with obesity.

While keeping the recommendations for the diabetes and obesity applications separate, the Expert Committee evaluated the applications together to better contrast possible differences between benefits and harms for the two conditions and understand the implications of coverage for the two cohorts of patients at global, regional and national levels. The Committee also recalled that previous applications (in 2017, 2021 and 2023) for inclusion of GLP-1 receptor agonists for use in the treatment of diabetes had been evaluated and not recommended.

Committee recommendations

The Expert Committee recognized that diabetes and obesity currently represent two major global health challenges, with both conditions reaching epidemic proportions in different populations and regions. According to a study by the NCD Risk Factor Collaboration, in 2022, there were an estimated 828 million adults globally living with diabetes. At the same time, the prevalence of obesity has increased globally – more than doubling in adults since 1990 – and now affecting more than 1 billion people. Growth in the prevalence of obesity is most rapid in low- and middle-income countries. Both diabetes and obesity are major contributors to mortality and morbidity, are responsible for substantial disability-adjusted life years and strain health systems worldwide. Notably, the relationship between obesity and diabetes is both causal and cyclical; excess adiposity significantly increases the risk of type 2 diabetes through mechanisms involving insulin resistance and chronic inflammation. Furthermore, diabetes and obesity together exacerbate the risk of cardiovascular diseases, forming a triad of interlinked conditions that influence each other and jointly account for a substantial proportion of preventable deaths. The Committee noted that 30% to 50% of people with type 2 diabetes have established cardiovascular disease and obesity, representing a large global cohort with this triad of comorbidities. The Committee also noted that for people with all three of these conditions, the risk of death is much higher than in people with either diabetes or obesity alone.

The Committee noted the evidence from multiple large-scale randomized controlled trials and systematic reviews that demonstrated the efficacy of GLP-1 receptor agonists and the GLP-1/GIP dual agonist tirzepatide in people with diabetes in improving glycaemic control, reducing the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), reducing the risk of end stage kidney disease, reducing all-cause mortality, improving health-related quality of life and promoting weight loss, compared with placebo. The Committee noted the consistency of benefits across studies. The Committee also acknowledged that, while some degree of benefit was possible in all patients irrespective of risk of cardiovascular diseases, patients with type 2 diabetes with known cardiovascular disease or chronic kidney disease are a high-risk subgroup that is likely to experience the most relevant benefit, with a 10-fold decreased risk of premature death compared with patients at low risk. The large difference in benefit between those at low risk and those at high risk for premature mortality is an important factor that could be used to identify those patients to be prioritized in the introduction of these medicines at the country level.

The Committee noted the evidence from the large systematic review demonstrating the efficacy of GLP-1 receptor agonists (particularly subcutaneous semaglutide) and tirzepatide in people with obesity for achieving clinically meaningful weight loss and improving quality of life, compared with lifestyle

modification alone. However, the Committee agreed that evidence of benefits in cardiovascular outcomes and mortality in people with obesity without diabetes was currently limited to a single, large, randomized controlled trial of semaglutide versus placebo. While the outcomes of this trial for cardiovascular outcomes were positive, there were more discontinuations due to adverse events in people receiving semaglutide. The Committee noted that the trial reported outcomes after almost 40 months of follow-up and considered that the available evidence on mortality outcomes was still at an early stage and limited. Refer to the summary for the addition of GLP-1 receptor agonists for use in adults in obesity for full details of the Expert Committee's recommendation for this indication.

Overall, the Committee considered that the magnitude of benefits and certainty of evidence for GLP-1 receptor agonists and tirzepatide were greater for people with diabetes than for people with obesity, particularly for important outcomes of cardiovascular events and mortality, upon which the Committee placed greater value than outcomes of glycaemic control and weight loss.

Considering the population of people with type 2 diabetes, the Committee identified people with comorbid established cardiovascular disease or chronic kidney disease as being the cohort for whom the net benefit of treatment was the greatest. The Committee then decided to include comorbid obesity (BMI ≥ 30 kg/m2) as an additional eligibility criterion, thereby establishing a defined high-risk cohort of people for whom these medicines should be listed as essential. The Committee's reasons for identifying a triple target population include: (i) obesity is a condition that can negatively affect both the mental and physical health of people with diabetes, stalling or worsening the health status; (ii) certain molecules within the pharmacological classes of GLP-1 receptor agonists and GLP-1/GIP dual agonists have an important effect on body weight, i.e. substantial weight reductions far exceeding the weight reductions associated with other hypoglycaemic agents on the EML (e.g. sodium-glucose cotransporter 2 inhibitors); and (iii) the need to highlight the importance of obesity as a public health priority one that requires effective treatment and commitment at both scientific and policy levels. The Committee acknowledged that although effective treatments for people with diabetes and established cardiovascular disease are already included on the Model List, these individuals remain at residual risk for future cardiovascular events. The addition of semaglutide and its therapeutic alternatives to existing therapies may offer further risk reduction, while also providing more pronounced weight loss compared with alretnatives such as SGLT-2 inhibitors.

The Committee noted that semaglutide, liraglutide, dulaglutide and tirzepatide were associated with important cardiovascular benefits in patients with type 2 diabetes. However, the Committee noted that there were important differences between these medicines for weight loss, with semaglutide and tirzepatide being associated with more relevant body weight reductions compared with the others. The Committee noted that the availability and use of semaglutide

and tirzepatide are constrained by price that currently limit their use to only well-resourced health-care systems.

The Committee acknowledged the current high price of these medicines and noted the reported cost-effectiveness ratios that exceed willingness-to-pay thresholds in many settings, particularly when used in low-risk patients. The Committee also noted the recent or upcoming patent expiry for liraglutide and semaglutide, which will introduce the possibility for biosimilar entry, increased competition and lower prices. The Expert Committee believed that substantial price reductions could be achieved with biosimilar entry and competition, given the size and universality of the market for these medicines. The Committee noted that when a large eligible patient population exists, robust biosimilar competition has consistently proven to be more reliable at sustainably reducing prices than other price-reduction mechanisms.

The Expert Committee therefore recommended the inclusion of semaglutide, dulaglutide, liraglutide and tirzepatide on the core list of the EML as add-on glucose-lowering therapy for adults with type 2 diabetes mellitus and both (i) established cardiovascular disease or chronic kidney disease; and (ii) obesity (BMI $\geq 30 kg/m^2$) which has a significant impact on their physical health and/or quality of life. This recommendation is made based on evidence of a meaningful and favourable balance of benefits to harms in this patient population. Listing is recommended for semaglutide with a square box, with dulaglutide, liraglutide and tirzepatide as specified therapeutic alternatives. The Committee's decision to recommend a square box listing for semaglutide, with dulaglutide, liraglutide and tirzepatide as therapeutic alternatives aims to foster competition among available alternatives. The Committee hoped that having multiple EML-listed options would serve to facilitate the rapid introduction of prequalified biosimilar formulations and would support countries in negotiating lower medicine prices and selecting the product that represent the best value option.

The Committee recommended the inclusion of these medicines in the core list to underscore the importance of their availability in the primary care setting. Type 2 diabetes and its complications, including obesity, are managed primarily in primary care. Delaying access by requiring hospital referral can reduce benefits associated with early intervention, adding costs and limiting availability in rural areas or underserved communities.

In recognition of the financial implications of including these medicines in national health systems at their current prices, particularly in resource-constrained settings, the Committee emphasized the importance of targeting use in the first instance to those patients in whom the greatest value health benefit can be realized. The Committee also recommended that WHO continue to monitor the evolving landscape of this class of medicines, including benefits associated with use in people with obesity, potential long-term toxicities and approval of oral formulations. The Committee also recommended that WHO work on existing

approaches for managing prices and evaluate alternative strategies to improve affordability and access to reduce the global burden of diabetes.

The Expert Committee highlighted that its recommendation provides countries with a practical strategy for rolling out GLP-1 receptor agonists in a fair and efficient manner. By prioritizing patients with type 2 diabetes and established cardiovascular or chronic kidney disease—those at highest risk of premature death and major adverse cardiovascular events—the recommendation aligns with principles of maximizing health benefits and reducing harm. This prioritization helps countries allocate limited resources to where the impact will be greatest. At the same time, the Committee recognized that countries with additional resources may consider extending access to other cohorts, such as adults with obesity and elevated cardiovascular risk but without diabetes, where evidence of benefit is emerging. Such a phased approach supports equity, prevents treatment disparities, and ensures that the introduction of these medicines contributes to reducing preventable mortality and morbidity.

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Section 22: Medicines for reproductive health and perinatal care

Changes to Section 22

The Expert Committee endorsed changes to Section 22 and the listing of medicines for medical abortion proposed by the WHO Department of Sexual and Reproductive Health and Research. The changes are summarized in Table 3 of the Executive summary.

Section 24: Medicines for mental and behavioural disorders

Methylphenidate – addition – EML and EMLc

Methylphenidate **ATC code: N06BA04**

Proposal

Addition of methylphenidate to the EML and EMLc for treatment of children and adolescents between the ages of 6 and 17 years with attention-deficit hyperactivity disorder (ADHD).

Applicant

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WHO technical department

The Department of Mental Health, Brain Health and Substance Use reviewed the application. The technical department referred to the recommendation on methylphenidate treatment in older children and adolescents with ADHD in the 2023 mhGAP guidelines and highlighted remarks made by the guideline group.

EML/EMLc

EML and EMLc

Section

24 Medicines for mental and behavioural disorders

Dose form(s) & strengths(s)

Capsule (extended-release): 10 mg to 60 mg (hydrochloride)

Tablet: 5 mg, 10 mg, 20 mg (hydrochloride)

Tablet (extended-release): 18 mg, 27 mg, 36 mg, 54 mg, 72 mg (hydrochloride)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application for the addition of methylphenidate to the EML and EMLc for the treatment of ADHD was considered by the Expert Committee in 2019. Listing was not recommended due to concerns about the quality and interpretation of the evidence for benefits and harms (*1*).

Another application for methylphenidate was considered by the Expert Committee in 2021. The Committee considered new evidence presented in the application from a 2018 network meta-analysis of trials evaluating the comparative efficacy and tolerability of medicines for ADHD, including, but not limited to, methylphenidate, in children, adolescents and adults (*2*). The Committee noted that most of the studies included in the network meta-analysis were judged to have an unclear or high risk of bias. In addition, few of the studies measured outcomes beyond 12 weeks of treatment, which the Committee considered was a major limitation, given that ADHD is a longer-term condition (*3*).

Regarding safety and harms, the network meta-analysis reported on the outcome of tolerability, defined as the proportion of patients who dropped out of studies due to adverse effects. The Committee considered that this outcome did not provide adequate information on the frequency and severity of specific adverse effects associated with methylphenidate use (*3*).

The Committee also considered that the true prevalence of ADHD was uncertain, because of variability in diagnostic approaches and the potential clinical overlap with other psychiatric illnesses. With the potential for both under- and over-diagnosis, it was therefore difficult to estimate the actual burden of disease (*3*).

The Committee noted that the 2016 WHO Mental Health Gap Action Programme (mhGAP) guidelines recommended that the use of stimulant medication must always be part of a comprehensive treatment plan that includes psychological, behavioural and educational interventions. Recommended first-line interventions for ADHD in the WHO mhGAP guidelines are non-pharmacological (environmental, behavioural and psychosocial). Referral to a specialist for consideration of methylphenidate is only recommended after non-pharmacological interventions have failed and the child is at least 6 years old. The Committee recognized that the availability of these recommended first-line interventions and specialists in the diagnosis and treatment of children with ADHD may be limited in many low- and middle-income countries. The Committee also noted advice from the WHO Department of Mental Health and Substance Use that the mhGAP guidelines were in the process of being reviewed at that time. It was noted that the review process would take into consideration

health-system capacity to: enforce and implement protocols for ADHD diagnosis; regulate the prescription and initiation of methylphenidate treatment; and ensure careful clinical monitoring of adverse effects, clinical response, adherence, treatment acceptability, requirements for dose adjustment, and risk of misuse, overmedicalization and overtreatment of behavioural problems in children (*3*).

The Committee also noted with concern the high prevalence of non-medical use and diversion of prescription stimulants, including methylphenidate. The Committee noted that methylphenidate is included in the list of psychotropic substances under international control. As such, methylphenidate is subject to import and export restrictions and other legal mechanisms aimed at limiting its use only for scientific and medical purposes to prevent diversion and misuse (*3*).

Overall, the Committee considered that even with the new evidence presented in the application, together with previously considered data, the benefit-to-harm ratio for the long-term use of methylphenidate remained uncertain. The Committee therefore did not recommend the inclusion of methylphenidate on the EML and EMLc. The Committee advised that for any future consideration for the listing of methylphenidate, the following would be informative: evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health-system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in resource-constrained settings (*3*).

Public health relevance

According to the 2021 Global Burden of Disease study, the estimated prevalence of ADHD in people aged 20 years or younger was 1.95% (uncertainty interval (UI) 1.34% to 2.78%), corresponding to almost 47 million (UI 32 million to 67 million) people. Prevalence data showed variation across WHO regions (from 0.87% in the African region to 3.74% in the Western Pacific region), and across country income levels (from 0.97% in low-income countries to 3.54% in upper-middle-income countries. Globally, in people younger than 20 years, ADHD was associated with almost 600 000 years lived with disability (*4*).

A diagnosis of childhood ADHD has been associated with impairment of quality of life, worse educational attainment, unemployment, criminality, increased risk of physical injuries and higher mortality (*5*–*10*). ADHD has also been associated with increased economic burden, with children diagnosed with ADHD being associated with higher costs than non-diagnosed counterparts from a societal perspective (*11*).

ADHD is a chronic condition that has variable courses during child development. Rates of persistence of the diagnosis from childhood and adolescence into early adulthood have been reported to be around 50% (*12*). For many children and adolescents with ADHD, symptoms may vary with age, leading

to periods of remission and recurrence (*13*, *14*). Thus, repeated assessments over time to assess the need for continued treatment are important.

Summary of evidence: benefits

The application presented a summary of the literature search performed and relevant evidence identified. The applicants prioritized evidence from systematic reviews and meta-analyses. Where these were unavailable, evidence from single randomized controlled trials and non-randomized and/or observational studies were presented. Studies published from 2022 onwards were highlighted, as earlier evidence had been presented in previous applications.

Long-term efficacy and effectiveness

Randomized controlled trials with treatment duration longer than 6 months

The 1999 Multimodal Treatment of ADHD study was a four-group, parallel-design randomized controlled trial in which 579 children with ADHD aged 7 to 9.9 years were randomized to receive medication management ($n = 144$), behavioural treatment ($n = 144$), combined treatment ($n = 145$) or community care ($n = 146$) for a period of 14 months (*15*). Of the 289 participants randomized to medication management (alone or in combination with behavioural treatment), 212 (73.4%) remained on methylphenidate for 14 months, with an additional 39 (13.5%) switching per protocol to another medication (mostly dextroamphetamine). Intention-to-treat analyses found that at 14 months participants on combined treatment experienced a greater decrease in: teacher-ratings of inattention (standardized mean difference (SMD) −0.45, 95% confidence interval (CI) −0.7 to −0.2); parent-ratings of inattention (SMD −0.57, 95% CI −0.81 to −0.320); hyperactivity–impulsivity (SMD −0.58, 95% CI −0.82 to −0.33); and aggression (SMD −0.42, 95% CI −0.66 to −0.17) compared with those receiving behavioural treatment alone. Combined treatment did not outperform behavioural treatment on teacher ratings of hyperactivity–impulsivity and aggression, classroom observer ratings of hyperactivity–impulsivity and aggression. By treatment endpoint, methylphenidate was administered at a mean daily dose of 31.2 mg in the combined treatment arm versus 37.7 mg in the medication arm. The largest treatment effects emerged during the first 50–100 days and were maintained until the study endpoint.

The application highlighted the following caveats to the results of this study. First, only around 73% of participants randomized to methylphenidate were maintained on this medication at the study endpoint, when recommendations for post-study care were made, with the remaining participants being switched (within study protocol) to other pharmacological or non-pharmacological interventions. This has an impact on the conclusions about methylphenidate specifically. Second, the medication management arm was intensive due to monthly 30-minute clinic visits and collection of parent and teacher ratings with

dose adjustments as needed; therefore, some effects of the intervention in this treatment arm may be due to non-specific effects of frequent doctor visits. Third, knowledge of the intervention may have influenced the outcome assessment.

Secondary analysis of data from the 14-month Multimodal Treatment of ADHD study evaluated the effectiveness of stimulant medication in treating irritability in children with ADHD (*16*). The results indicated that medication management was superior to behavioural management but did not differ from community care for reducing irritability.

A randomized trial in Mexico compared the efficacy of omega-3/6 fatty acids, methylphenidate, or a combination of the two, for 12 months in 90 children aged 6 to 12 years with ADHD (*17*). Methylphenidate was administered in a flexible-dose design with mean dose of 0.8 mg/kg a day. In the intention-to-treat analyses, children taking combination treatment showed more improvement in ADHD symptoms reported by parents (SMD −0.51, 95% CI −1.03 to 0.00) compared with those only taking omega-3/6. Treatment effects of methylphenidate were seen initially in the first 3 months and then maintained throughout the follow-up until 12 months. Limitations of the study included lack of blinding, lack of statistical power and different rates of discontinuation across arms due to the health status of participants, which may contribute to bias. Specifically, 7% of children receiving combination therapy and 20% of those receiving omega-3/6 withdrew from the study due to adverse events or no efficacy.

Other randomized controlled trials

A 2019 randomized, double-blind, placebo-controlled discontinuation study evaluated the continued effects of methylphenidate in 94 children and adolescents aged 8 to 18 years who had received methylphenidate treatment for more than 2 years (*18*). Participants were randomly assigned to continued treatment for 7 weeks with extended-release methylphenidate or gradual withdrawal over 3 weeks to 4 weeks of placebo. The primary outcome measure was investigator-rated ADHD rating scale total score. Secondary outcomes included investigator-rated Clinical Global Impressions Improvement Scale scores and the Conners' Teacher Rating Scale-Revised: Short Form score. From baseline to 7 weeks, significant differences were seen between discontinuation and continuation groups favouring the continuation group for ADHD rating scale total scores (mean difference (MD) −4.6, 95% CI −8.7 to −0.6), and Conners' Teacher Rating Scale ADHD index scores (MD −6.6, 95% CI −9.5 to −3.7). Investigator-rated worsening in overall functioning was reported for 40.4% and 15.9% of participants in the discontinuation and continuation arms, respectively. Other studies incorporating randomized discontinuation of methylphenidate have also reported an overall worsening of symptoms after discontinuation (*19*). The length of time that children had been on methylphenidate varied considerably between studies (from 1 year to 1 week). Additionally, in most studies, a minority

of children and adolescents with ADHD did not relapse or deteriorate when taken off medications for ADHD. The findings are limited by features such as participants perhaps being functionally unblinded due to subject-perceived effects of stopping the medicine.

Observational studies

An observational nationwide cohort study in Sweden evaluated individuals aged 6 to 64 years with an incident diagnosis of ADHD between 2007 and 2018, who were medication naive before diagnosis (*20*). Individuals were followed up from diagnosis until either death, emigration, 2 years after ADHD diagnosis or until the study end date of 31 December 2020. Outcomes assessed were all-cause mortality, natural-cause and unnatural-cause mortality. Among 145 578 individuals with ADHD, 84 204 started medication for the condition. The median age at diagnosis was 17.4 years. A significantly lower rate was found favouring the initiation group of all-cause mortality (risk difference (RD) −8.9 per 10 000, 95% CI −17.3 to −0.6; hazard ratio (HR) 0.79, 95% CI 0.70 to 0.88), and unnatural-cause mortality (RD −7.4 per 10 000, 95% CI −14.2 to −0.5; HR 0.75, 95% CI 0.66 to 0.86) during the 2-year follow-up period. No significant difference was seen between groups for natural cause mortality (RD −1.6 per 10 000, 95% CI −6.4 to 3.2; HR 0.86, 95% CI, 0.71 to 1.05). In subgroup analyses, a significant association with lower rates of all-cause and unnatural-cause mortality was also observed for individuals aged 6 to 24 years.

A population-based retrospective cohort study in Canada assessed the association between ADHD medication use and the risk of all-cause mortality and unintentional injuries leading to emergency department or hospital admission in 217 192 individuals aged ≤ 24 years with ADHD between 2000 and 2021 (*21*). Episodes of ADHD medication use were associated with reduced risk of all-cause mortality (adjusted HR 0.61, 95% CI 0.48 to 0.76), unintentional injuries leading to hospitalization (adjusted HR 0.71, 95% CI 0.68 to 0.75) and unintentional injuries leading to emergency department visits (adjusted HR 0.75, 95% CI 0.74 to 0.77).

Systematic reviews

A 2020 systematic review and meta-analysis evaluated the effects of ADHD medications on functional outcomes using literature from large population-based databases and registries published before January 2019 (*22*). The review included 40 articles in a qualitative review, of which 21 were suitable for quantitative meta-analysis. Pooled results of the meta-analysis found that ADHD patients taking stimulants and/or non-stimulants had significantly decreased odds of developing mood disorders (odds ratio (OR) 0.80, 95% CI 0.76 to 1.84), accidents and injuries (OR 0.72, 95% CI 0.59 to 0.87) and poor academic outcomes (OR 0.80, 95% CI 0.76 to 0.84). For outcomes of suicidality, substance use disorders, criminality and traumatic brain injury, risks were reduced but were not statistically significant.

Short-term efficacy

Methylphenidate versus placebo/no treatment

A 2023 Cochrane systematic review of 212 randomized controlled trials (16 302 participants) evaluated the benefits and harms of methylphenidate versus placebo or no treatment in children and adolescents aged 18 years and younger with ADHD (*23*). Most trials were conducted in high-income countries and about 40% were fully or partly industry funded. The mean age of participants was 9.8 years and the mean duration of treatment across all trials was 28.8 days. This review was an update of the review conducted in 2015 of 185 randomized controlled trials (12 245 participants) which had been presented in previous applications for methylphenidate (*24*).

Compared with placebo or no treatment, the updated review found very-low-certainty evidence that methylphenidate may improve teacher-rated ADHD symptoms (SMD −0.74, 95% CI −0.88 to −0.61; 21 randomized controlled trials, 1728 participants), corresponding to a mean difference of −10.58 points (95% CI −12.58 to −8.72) on the ADHD rating scale (a change of 6.6 points on this scale is considered the minimal clinically relevant difference). The quality of evidence was downgraded two levels due to high risk of bias, and one level due to moderate statistical heterogeneity. In a subgroup analysis of trials at low and high risk of bias, no evidence was found that the risk of bias influenced the effect estimate.

For the outcome of independent assessor-rated ADHD symptoms, evidence of benefit was found favouring methylphenidate (SMD −1.10, 95% CI −1.44 to −0.77; 22 randomized controlled trials, 3724 participants), corresponding to an MD of −15.7 points (95% CI −14.7 to −7.9) on the ADHD rating scale. When two trials considered outliers with unrealistically high effect sizes were removed, the SMD was −−0.62, 95% CI −0.79 to −0.46, corresponding to a mean difference of −8.7 points on the ADHD rating scale. In a subgroup analysis of trials at low and high risk of bias, the benefit of methylphenidate was lower in trials with low risk (SMD −0.40, 95% CI −0.78 to −0.03; four randomized controlled trials, 942 participants) than in those with high risk (SMD −1.30, 95% CI −1.70 to −0.89; $I^2 = 96\%$; 18 trials, 2782 participants). The mean difference in ADHD rating scale scores from trials with low risk of bias (one randomized controlled trial, 253 participants) was −5.7 points (95% CI −10.4 to −0.4) and below the minimal clinically relevant difference. Another subgroup analysis found lower effects of methylphenidate in long-term trials (SMD −0.35, 95% CI 0.61 to −0.08; one randomized controlled trial, 221 participants) than in short-term trials (SMD −1.15, 95% CI −1.50 to −0.80; 21 randomized controlled trials, 3503 participants). The mean difference in ADHD rating scale scores from long-term trials was −5.0 points (95% CI −8.7 to −1.1) and below the minimal clinically relevant difference (*23*).

For the outcome of parent-rated ADHD symptoms, evidence was found of benefit favouring methylphenidate (SMD −0.63, 95% CI −0.76 to −0.50; 27

randomized controlled trials, 2927 participants), corresponding to a mean difference of −9.0 points on the ADHD rating scale. In a subgroup analysis of trials at low and high risk of bias, no evidence was found that risk of bias influenced the estimate of effect (*23*).

The application presented issues raised by researchers about the ratings of the certainty of evidence from the Cochrane. They were considered to be overly stringent in downgrading the quality of evidence due to risk of bias and heterogeneity. There is debate about: the extent to which lack of blinding contributes to exaggerated comparative treatment effects for subjective outcomes; that the lack of differences between randomized controlled trials at different risk of bias could indicate a functional unblinding due to adverse events; and the different measures of heterogeneity (tau^2 and I^2) producing different outcomes.

A 2022 meta-analysis of 31 studies (804 participants) evaluated dose-dependent effects of methylphenidate on neurocognitive functions in children and adolescents aged 5–18 years with ADHD (*25*). Duration of methylphenidate treatment ranged from 1 to 21 days. All the studies included were rated as having a low risk of bias. Outcomes assessed included variability in baseline response speed, non-executive memory and executive memory, inhibitory control, and cognitive flexibility. ADHD symptoms were assessed if available. Methylphenidate was reported to have beneficial effects on all neurocognitive functions assessed, with SMDs for effect sizes ranging from 0.20 (95% CI 0.03 to 0.38) for executive memory to 0.73 (95% CI 0.60 to 0.85) for variability in responding. Methylphenidate was associated with benefit in terms of aggregated parent and teacher symptom rating scales (SMD 0.95, 95% CI 0.78 to 1.14). Significant linear dosing effects were found for ADHD symptoms, baseline speed, variability in responding and non-executive memory. No dosing effects were found for executive memory, inhibitory control or cognitive flexibility.

A 2018 systematic review and meta-analysis of 34 studies (1777 participants) evaluated the effects of methylphenidate compared with placebo on academic productivity and accuracy in children with ADHD (*26*). Outcomes significantly favoured methylphenidate for: math accuracy (RD 3%, 95% CI 1.2% to 4.8%; 29 studies, 1528 participants); math productivity (RD 7.8%, 95% CI 4.3% to 11.2%; 17 studies, 912 participants); and number of reading items attempted (SMD 0.47, 95% CI 0.30 to 0.64; five studies, 100 participants). For reading accuracy, a non-significant treatment effect was observed favouring methylphenidate (RD 6.2%, 95% CI −0.9% to 13.4%; nine studies, 207 participants). No evidence of heterogeneity or publication bias was observed. Of note, these results were based on studies of short duration (between 1 and 7 days) and do not test cumulative impact of productivity on longer term achievement. Additionally, academic testing, by its nature, includes high levels of attention and reinforcement in the moment and reduces the opportunity to observe effects of medication.

Comparison with other medications for ADHD

A 2018 systematic review and network meta-analysis evaluated the comparative efficacy and tolerability of pharmacological interventions for ADHD, including methylphenidate, versus each other or placebo (*2*). The review included 133 randomized controlled trials, including 81 (14 346 participants) in children and adolescents aged 5–17 years. The efficacy analysis was based on 10 068 children and adolescents. In head-to-head comparisons, for the outcome of ADHD core symptoms rated by clinicians closest to 12 weeks, methylphenidate was superior to atomoxetine (SMD −0.22, 95% CI −0.39 to −0.05; low-quality), but inferior to amphetamines (SMD 0.24, 95% CI 0.05 to 0.44; low-quality evidence. No significant differences were seen between methylphenidate and: bupropion (SMD −0.18, 95% CI −0.9 to 0.54, very-low-quality evidence); clonidine (SMD 0.07, 95% CI −0.42 to 0.56; very-low-quality evidence); and guanfacine (SMD 0.11, 95% CI −0.13 to 0.34; low-quality evidence). For ADHD core symptoms rated by teachers, no differences were seen between methylphenidate and atomoxetine, bupropion or guanfacine. For tolerability, measured as the proportion of participants who discontinued treatment due to adverse events, amphetamines and guanfacine were significantly inferior to placebo. No significant differences were seen between other pharmacological interventions and placebo for this outcome.

Summary of evidence: harms

In response to the concerns raised by the previous Expert Committee, the application focused on adverse events that occur in the longer term with methylphenidate.

Long-term safety

In the above-mentioned randomized controlled trials of long-term methylphenidate treatment (*15*, *17*) and an observational study of long-term safety of methylphenidate treatment (ADDUCE) (*27*), no association was found between methylphenidate treatment and serious adverse events.

Effects on growth

A 2021 systematic review and meta-analysis of 18 observational studies (4868 participants) evaluated the association between long-term (> 6 months) methylphenidate treatment and growth (*28*). The average daily dosage of methylphenidate across studies was about 30 mg. The meta-analyses indicated statistically significant pre–post differences in height Z-score (SMD 0.27, 95% CI 0.38 to 0.16) and weight Z-score (SMD 0.33, 95% CI 0.44 to 0.22). These estimates translated to slowing of height gain by about 1.39 cm and of weight gain by about 1.96 kg for a 10-year-old boy over a 2-year period. The most prominent effects on weight were seen in the first 12 months of treatment, and on height within the first 24–30 months.

A 2020 study estimated the long-term associations of stimulant medication on growth trajectories from childhood to adulthood in the Multimodal Treatment of ADHD study (29). Over a period of 16 years, 568 children with ADHD and 258 controls were assessed eight times. The study found that children consistently treated with methylphenidate and other stimulants from ages 7–9.9 years through to adolescence were on average 4.06 cm shorter by mean age 24.7 years than children who were not treated and 2.74 cm shorter than children who were inconsistently treated across the same period.

The ADDUCE study was a naturalistic, longitudinal, controlled study that evaluated the long-term safety of methylphenidate in 1410 children and adolescents aged 6–17 years with ADHD in 27 European child and adolescent mental health centres (27). Participants were recruited into three cohorts: medication-naive ADHD patients who intended to start methylphenidate treatment (methylphenidate group, $n = 756$), medication-naive ADHD patients who did not intend to start any ADHD medication (no-methylphenidate group, $n = 391$) and a control group without ADHD ($n = 263$). The study found no difference in height velocity at any time point between the methylphenidate and no-methylphenidate groups. A slowing in weight velocity was observed in the methylphenidate group only at the 6-month time point. No differences between groups were observed for body mass index.

Cardiovascular safety

A 2012 study estimated the long-term associations of stimulant medication on blood pressure and heart rate in the Multimodal Treatment of ADHD study (30). At the study endpoint (14 months), children who received combined treatment had a significantly higher heart rate than those treated with behavioural therapy alone (mean (standard deviation) 84.6 (12.2) versus 79.1 (12.0); $P = 0.01$). No difference was observed thereafter. No treatment effects were observed on systolic or diastolic blood pressure.

A 2022 systematic review and meta-analysis of 19 observational studies (3 931 532 participants, including children, adolescents and adults) evaluated possible associations between ADHD medications (including methylphenidate) and the risk of a range of cardiovascular events (31). Fourteen of the studies were cohort studies and the median follow-up time was 1.5 years (range 0.25 to 9.5 years). ADHD medication use was not significantly associated with an increased risk of any cardiovascular events in children and adolescents (pooled adjusted relative risk (RR) 1.18, 95% CI 0.91 to 1.53) or in older age cohorts.

The ADDUCE study reported a greater increase in systolic and diastolic blood pressure in the methylphenidate group compared with the no-methylphenidate group at 6, 12 and 24 (but not 18) months from baseline. Pulse rate increased more in the methylphenidate group than in the no-methylphenidate group at 12 and 24 months, but not at 6 or 18 months (27).

A 2023 Swedish register-based case–control study evaluated the long-term risk of cardiovascular diseases associated with ADHD medications (including methylphenidate) in 278 027 individuals aged 6 to 64 years (*32*). A total of 10 388 individuals with ADHD who had a cardiovascular event were demographically matched with 51 672 controls with ADHD and without a cardiovascular event. Both groups had a median follow-up period of 4.1 years. Methylphenidate was the dispensed medication in 76.2% and 76.1% of cases and controls, respectively. The study found evidence for an increased risk of cardiovascular disease with longer cumulative duration of ADHD medication use compared with non-use, for example, at 0 to ≤ 1 year (adjusted OR 0.99, 95% CI 0.93 to 1.06) and at > 5 years (adjusted OR 1.23, 95% CI 1.12 to 1.36). Longer cumulative duration of ADHD medication was also associated with a significantly increased risk of hypertension and arterial disease, but not arrhythmia, heart failure, ischaemic heart disease, thromboembolic disease or cerebrovascular disease.

A 2024 Swedish retrospective, population-based cohort study investigated the association between cardiovascular events and short-term methylphenidate use in 252 382 participants aged 12 to 60 years with ADHD (*33*). Rates of cardiovascular events were compared 1 year before methylphenidate treatment and 6 months after starting methylphenidate treatment. The posterior probabilities of at least a 10% increased risk of cardiovascular events were 70% and 49% for methylphenidate and control groups, respectively. The probability of finding a methylphenidate-related difference in risk decreased when considering risk levels of 20% or larger. This study did not consider children younger than 12 years and lacked data on dosage effects (which have emerged as important factors in other studies of cardiovascular risk).

Psychiatric/neurological adverse events

In the ADDUCE study, the prevalence of suicidality (ideation or behaviour) decreased for all groups from baseline to 24 months to 3.17%, 0.77% and 0.76% in the methylphenidate, no-methylphenidate and control groups, respectively. No significant between-group differences were seen after adjusting for baseline differences. Parent- and child-ratings of mood improved in those taking methylphenidate compared with the no methylphenidate group from baseline to 24 months. The prevalence of psychotic-like symptoms decreased from baseline to 24 months, with no significant difference between groups (*27*).

Short-term safety

The application also presented a summary of evidence for the safety of methylphenidate from short-term treatment studies.

Non-medical use and diversion

A 2020 systematic review of 111 studies evaluated the non-medical use and diversion of prescription stimulants (*34*). Of the studies included, 86 addressed the epidemiology of non-medical use and diversion. Rates of these behaviours varied widely across studies and generally focused on older adolescents and young adults. The prevalence rates of non-medical use ranged from 2.1% to 58.7% and diversion rates from 0.7% to 80.0%. Academic and occupational performance enhancement were the most commonly cited motivations.

The 2018 College Prescription Study was a multi-institutional survey of the non-medical use of prescription medicines in 19 539 undergraduate and graduate students and those in professional programmes in the United States (*35*). Among respondents, 9.1%, 9.4% and 15.9% reported non-medical use of pain medications, sedatives and stimulants, respectively. Of these, 44.6%, 57.9% and 62.9% reported non-medical use of pain medications, sedatives and stimulants, respectively in the previous 12 months. Among non-medical users of stimulants, 47% reported use 1–9 times in the previous 12 months.

A 2023 cross-sectional study used survey data to estimate the prevalence and association between stimulant therapy for ADHD and non-medical use in United States secondary-school students (*36*). From datasets collected across 3284 schools between 2005 and 2020, among 231 141 students, the mean prevalence of non-medical use of prescription stimulants in the past year was 5.7% at the school level and 6.0% at the individual level. Different variables were associated with non-medical use, for example, other substance use such as marijuana and alcohol, parental college education, greater percentage of student body identifying as white and greater percentage of student body using prescribed stimulant medications).

A 2023 survey study of drug use in United States secondary school students found the prevalence of non-medical use of methylphenidate declined from 2001 to 2021: from 2.9% to 0.6% of eighth graders, 4.8% to 0.5% of 10th graders and from 5.1% to 0.6% of 12th graders (*37*).

Most non-medical stimulant use has been associated with no, or minor, medical effects. However serious adverse events can occur, particularly when administered by non-oral routes for example, injection or nasal inhalation (*38*).

Methylphenidate is a controlled substance in many countries and its prescribing and dispensing are subject to regulatory restrictions that aim to minimize non-medical use and diversion including:

- special training and licensing requirements for prescribing;
- monitoring of prescription rates by regulatory authorities to flag excessively high, unexplained rates of prescription;
- inability to issue refill prescriptions;

- requirement for regular monitoring and ongoing assessments of the need for the medication;
- prescription of formulations that may have less potential for non-medical use.

Additionally, many other strategies have been offered in the clinical and research literature, by government agencies and professional organizations, in studies testing reduction of non-medical use and diversion (e.g. use of extended-release instead of immediate-release formulations) (*34*, *39*–*41*) and in studies testing training programmes for physicians designed to help them prevent or reduce stimulant diversion and misuse (*42*, *43*).

Risk of later substance use after stimulant treatment

The Multimodal Treatment of ADHD study and other observational studies indicate that there is no evidence of an association between methylphenidate use in children with ADHD and an increased risk for substance use in adolescents and young adults (*44*–*46*). Large epidemiological studies have found protective effects for substance use outcomes of medications for ADHD in which within-subject analyses have compared medicated and unmedicated periods, allowing control for confounding by indication (*46*). For example, in an analysis of commercial health-care claims in the United States between 2004 and 2014 for more than 2.9 million adolescents and adults with ADHD, male and female patients had 35% and 31%, respectively, lower odds of concurrent referrals to emergency departments for substance-related events when receiving medication (*47*).

Data on the progression to misuse among young people prescribed stimulants from the Monitoring the Future study found that initiation of stimulant treatment for ADHD in childhood was not associated with an elevated risk of substance use, defined as cocaine, methamphetamine or prescription stimulant misuse in adolescence. However, start of stimulant treatment at older ages (≥ 10 years) and for shorter duration was associated with higher odds of past-year cocaine or prescription stimulant misuse in adolescence than those starting treatment in childhood. However, causal relationships could not be concluded based on the methodology (self-reported survey, retrospective data). In addition, it is not possible to account for confounders that might drive late initiation of treatment.

Additional evidence

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WHO guidelines

The 2023 WHO mhGAP guideline for mental, neurological and substance use disorders includes the following conditional recommendation (low-certainty evidence) for methylphenidate in the treatment of ADHD (*48*).

For children 6 years old and older and adolescents who have an attention deficit hyperactivity disorder (ADHD) diagnosis, methylphenidate may be considered, provided:

- ADHD symptoms are still causing persistent significant impairment in at least one domain of functioning (education, interpersonal relationships, occupation), after the implementation of environmental modifications in schools, at home or in other relevant settings;
- a careful assessment of the child/adolescent has been conducted;
- the child/adolescent and the caregivers, as appropriate, have been informed about ADHD treatment options and supported in decision-making;
- methylphenidate prescription is made by, or in consultation with, a specialist.

The guideline highlights the following remarks with regard to methylphenidate treatment.

- Treatment should be offered only in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms, functioning, well-being and participation of children and adolescents with ADHD.
- Treatment should be combined when possible with brief parent behavioural therapies.
- Children and adolescents receiving treatment should be maintained under close clinical monitoring for improvement in symptoms and prevention of adverse effects.
- A specialist care provider trained in management of ADHD should reassess the child/adolescent's management plan for ADHD at least once a year.
- The rationale for specialist assessment before prescription of methylphenidate is that diagnosis of ADHD requires specialist clinical judgement especially given the risks of misuse.

The guideline also includes specific considerations with regard to research gaps and implementation considerations.

- Strengthened intervention designs are needed with long-term follow-up to ascertain lasting intervention benefits, harms and acceptability in children and adolescents.
- More evidence needs to be made available on protocol adherence, misuse/safety, and treatment satisfaction when treatment with methylphenidate is prescribed and monitored in primary health-care settings.
- It is Important to consider the health system's capacity to enforce and implement protocols for ADHD diagnosis.

Costs/cost–effectiveness

The application presented prices of methylphenidate 10 mg tablets in different countries. The prices per unit (tablet) ranged from 0.03 United States dollars (US$) in Viet Nam to US$ 0.90 in Malaysia. No price information was presented for the other strengths or for the extended-release formulations of methylphenidate also proposed for inclusion on the Model Lists. The application noted that costs may vary depending on the formulation, manufacturer or both.

No new evidence of cost–effectiveness were presented, beyond that already considered by the Expert Committee in previous applications.

In 2019, the Expert Committee acknowledged that methylphenidate appeared to be low cost and affordable, but considered that no conclusions could be drawn on the cost–effectiveness of the medicine given the considerable uncertainty in the estimates of benefits and harms (*1*).

Availability

The application reported that methylphenidate is approved in over 70 jurisdictions globally and is included on the national essential medicines lists of more than 50 countries.

Other considerations

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Committee recommendations

The Expert Committee acknowledged that attention-deficit hyperactivity disorder (ADHD) has a substantial prevalence in children and adolescents globally, and was associated with substantial disability, including reduced quality of life, poorer educational attainment, higher unemployment, increased risk of injury and higher mortality. The Committee also recognized that ADHD

was also associated with increased economic burden for patients, caregivers and health systems.

The Committee recalled the recommendation of the 2021 Expert Committee to not include methylphenidate on the Model Lists because of enduring uncertainty in the benefit-to-harm ratio for the long-term use of the medicine. The 2021 Committee also recommended that any future consideration of methylphenidate should address evidence for the effectiveness and safety of methylphenidate in the treatment of ADHD of at least 52 weeks duration; outcomes of the revision of the WHO mhGAP guidelines; and evaluation of health system capacity to provide appropriate diagnostic, non-pharmacological and pharmacological treatment and monitoring in low-resource settings.

The 2025 Expert Committee appreciated the efforts of the applicants of the current application in presenting evidence and information addressing the 2021 Committee's recommendation.

In consideration of the evidence presented in the current application for longer-term efficacy and safety of methylphenidate, the Committee noted that randomized trials evaluating long-term treatment (> 6 months) were few and all had some methodological limitations. Selected pharmacoepidemiologic studies presented some real-world evidence for benefit in functional outcomes, reductions in all-cause mortality and unintentional injuries associated with long-term use of methylphenidate, however these studies also had intrinsic methodological limitations.

The Committee noted in particular the findings of the 1999 Multimodal Treatment of ADHD study, in which ADHD treatment with stimulant medication (not limited only to methylphenidate) was associated with greater improvements in ADHD symptoms when compared to behavioural management over a period of 14 months, as rated by parents, teachers or independent investigators. Stimulant treatment was not associated with an increase in serious adverse events. The Committee also noted evidence identified during the review process from follow-up analyses of the Multimodal Treatment of ADHD study that showed that the magnitude of benefit of stimulant treatment compared to behavioural management seen at 14 months attenuated over time (after 2 years, 3 years, and into adulthood). The Committee noted that at longer follow-up the advantage associated with methylphenidate in symptom control was not retained when compared with other strategies, including behavioural therapy alone or community care. The Committee was unable to discern if the loss in sustained benefits was due to tolerance, less adherence, crossover between different strategies, and if the change in effectiveness was associated with characteristics of the children and adolescents or of the syndrome, such as baseline severity.

With regard to long-term safety, the Committee noted mixed evidence of a potential association between methylphenidate use and effects on growth (weight and height), and potential for cardiovascular adverse effects.

The Committee considered the conditional recommendation in the 2023 WHO mhGAP guidelines, based on low-certainty evidence, that methylphenidate may be considered for use in children (from 6 years) and adolescents with ADHD under clearly specified circumstances. The Committee considered that the mhGAP guidelines provide an important framework for supporting and increasing health system capacity to ensure the appropriate use of methylphenidate in children and adolescents. The Committee noted that the guidelines highlight, amongst other things, the limited evidence on efficacy and tolerability of methylphenidate beyond 12 weeks of treatment, that specialist reassessment of the patient's ADHD management plan should occur at least once per year, and the need for methylphenidate treatment to be offered only in the context of a comprehensive management plan.

The Committee expressed concern regarding the current capacity of some health systems to ensure appropriate diagnosis, treatment (both pharmacological and non-pharmacological), and management of ADHD, particularly in low- and middle-income settings, where reported rates of mental health workers for children and adolescents are low, and among whom specialist psychiatrists are a small minority.

The Committee acknowledged that methylphenidate is widely recommended and used in many countries as the standard of care for children and adolescents with ADHD and has wide regulatory approval and market availability. Furthermore, it is already included in the national essential medicines lists of some countries. The Expert Committee emphasized the need for countries listing methylphenidate to ensure that that is used within the context of comprehensive ADHD diagnosis, management and treatment services, initiated and overseen by a specialist, and only following inadequate response to recommended first-line, non-pharmacological interventions.

Based on these considerations, the Expert Committee did not recommend the inclusion of methylphenidate on the EML and EMLc for the treatment of children and adolescents with ADHD because of limitations in the available evidence of benefits and safety of long-term use, which reduced confidence in the estimates of prolonged beneficial effect.

The Committee further emphasized the critical need for funding and conducting rigorous research on methylphenidate and other stimulant medications. Future studies should prioritize large-scale, active placebo-RCTs with extended follow-up periods exceeding 52 weeks to adequately assess long-term efficacy and safety. While research in both adults and younger populations is important, the Committee highlighted that children and adolescents should be prioritized, as they are less able to independently evaluate treatment needs and perceived benefits compared to adults, who can make more informed choices weighing benefits against harms. The use of an active placebo is essential

to maintain blinding, which is fundamental for unbiased results in RCTs, particularly when outcomes rely on psychometric scales or observer ratings. This is because methylphenidate and other stimulants often produce immediate and noticeable effects—such as mild euphoria, reduced appetite, insomnia, headache, or anxiety—that can reveal treatment allocation and artificially inflate estimates of both benefits and adverse effects when compared to inactive placebos.

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24.1 Medicines used in psychotic disorders

Aripiprazole – addition – EML

Aripiprazole **ATC code: N05AX12**

Proposal

Addition of aripiprazole once-monthly long-acting injection to the core list of the EML as a therapeutic alternative to paliperidone once-monthly long-acting injection for maintenance treatment of schizophrenia in adults.

Applicant

Otsuka America Pharmaceutical Inc., Princeton, NJ, United States of America

WHO technical department

The Department of Mental Health, Brain Health and Substance Use reviewed and provided comments on the application. The technical department highlighted that aripiprazole long-acting injection was similar to other long-acting injection antipsychotics currently included on the EML (risperidone and paliperidone) for clinical efficacy and acceptability. However, aripiprazole long-acting injection may have advantages over the others in terms of tolerability (less weight gain), handling and storage. The technical department also advised that current costs were high and availability in low- and middle-income countries was limited. Aripiprazole long-acting injection is not currently included in the WHO mhGAP guidelines and the technical department did not think that there was a compelling case for the inclusion of aripiprazole long-acting injection on the EML at this time.

EML/EMLc

EML

Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Powder and solvent for intramuscular injection: 300 mg, 400 mg in prefilled syringe and single dose vial

Core/complementary

Core

Individual/square box listing

Square box listing in which aripiprazole is a specified therapeutic alternative to the representative medicine, paliperidone.

Background

Aripiprazole long-acting injection has not previously been evaluated for inclusion in the EML.

In 2021, the Expert Committee recommended the addition of paliperidone once-monthly long-acting injection to the core list of the EML for maintenance treatment of schizophrenia in adults stabilized on oral therapy. A square box listing was recommended specifying risperidone long-acting injection as a therapeutic alternative. The Committee considered that long-acting injectable antipsychotic medicines were a valuable treatment option to increase adherence to treatment and reduce relapse in adults with schizophrenia and related psychotic disorders. The Committee also noted with concern the uncertainty of current and future availability of fluphenazine injection, which was the only long-acting injectable antipsychotic medicine included on the EML at that time and considered that the availability of alternative medicines would be important to meet the public health need for such treatments. The Committee noted that long-acting injectable antipsychotic medicines are an established treatment option for schizophrenia and are recommended in existing WHO Mental Health Gap Action Programme (mhGAP) guidelines. In particular, the Committee acknowledged that long-acting injectable antipsychotic medicines are useful in low-resource settings, where many factors might impede regular monitoring and follow-up of patients. The Committee noted that the available data suggested benefits of long-acting injectable antipsychotic medicines versus oral antipsychotic medicines in preventing hospitalization or relapse, especially in populations with low treatment adherence. The effectiveness and overall safety of first-generation and second-generation antipsychotic medicines were similar. The availability of agents with different side-effect profiles may support the selection of one treatment over another given a patient's clinical status and vulnerabilities (*1*).

In 2023, the Expert Committee considered an application for the inclusion of paliperidone 3 monthly long-acting injection on the EML for maintenance treatment of schizophrenia. The 2023 Committee recognized that long-acting injectable antipsychotic medicines were an important treatment option for some patients with schizophrenia. It recalled the recommendation made by the 2021 Expert Committee to include paliperidone once-monthly long-acting injection on the EML for this indication, with risperidone long-acting injection as a therapeutic alternative among second-generation antipsychotics. The Committee

also noted the separate application to the 2023 meeting proposing therapeutic alternatives to long-acting injections of first-generation antipsychotics. The Committee noted that compared with the 1 month formulation, the 3-month formulation had evidence of similar clinical efficacy and safety and may offer advantages to patients in terms of fewer injections. However, the Committee noted that the 3-month formulation was recommended for use only in patients who had been adequately treated with the once-monthly formulation and demonstrated benefit from and tolerance to it for at least 4 months. The Committee was therefore concerned that both strength formulations would need to be available for appropriate treatment and considered that the more limited availability of the 3-month formulation in low- and middle-income countries would be problematic. In addition, the Committee noted that the 3 month formulation was more highly priced and was not yet available in generic forms, nor included in current WHO mhGAP guidelines. Based on these considerations, the Expert Committee did not recommend the inclusion of paliperidone 3-month long-acting injection on the EML for maintenance treatment of schizophrenia (*2*).

Oral aripiprazole was included in the EML in 2023 as one of four therapeutic alternatives to oral risperidone for the treatment of schizophrenia, in alignment with recommendations in the 2023 WHO mhGAP guideline (*2*).

Public health relevance

Schizophrenia is a chronic, complex, progressive and heterogeneous psychiatric disorder that typically manifests behaviourally in late adolescence or early adulthood (*3*,*4*). It leads to psychosis and significant disability, affecting personal, family, social, educational and occupational functioning (*5*). People diagnosed with schizophrenia often face stigma, discrimination and human rights violations (*5*,*6*).

According to the Global Burden of Disease study, the incidence of new schizophrenia cases rose by 37% from 1990 to 2019, reaching 1.3 million individuals. The age-standardized global incidence of schizophrenia was 16.31 per 100 000 individuals in 2019 and showed considerable geographic variation. The age-standardized global prevalence of schizophrenia in 2019 was reported to be 287.4 per 100 000 individuals (*7*). Schizophrenia was associated with the highest percentage increase in the prevalence rate compared with other mental disorders between 1990 and 2019 in low- and middle-income countries. A study conducted to determine the burden of mental disorders in Middle Eastern and North African countries determined that the prevalence of schizophrenia increased by 33.5% between 1990 to 2019 (*8*).

Schizophrenia was ranked the 20th leading cause of years lived with disability (YLDs) within mental health disorders in 2019. Schizophrenia accounted for the third largest proportion of disability-adjusted life years (DALYs) due to mental health disorders in 2019, at 12.2% (*7*). The rate of DALYs due to mental

disorders in low- and middle-income countries are increasing, with a 13.9% increase seen over 30 years. Among all mental disorders, schizophrenia had the third highest increase, with a 33.0% rise in DALY rates (*8*).

Schizophrenia has one of the highest mortality risks among psychiatric disorders, with a 2.9 fold increase in all-cause mortality, and individuals with schizophrenia die 15–20 years earlier than the general population (*9*). A 2017 systematic review and meta-analysis investigating years of potential life lost and life expectancy in schizophrenia reported that the overall weighted global average life expectancy for persons with schizophrenia was 64.7 years and was lower for men than women (59.9 years versus 67.6 years). The review also reported that life expectancy was the lowest in Asia and Africa, indicating disparities in health outcomes and access to health-care services compared with other regions (*10*).

Summary of evidence: benefits

Systematic reviews

A 2021 systematic review and meta-analysis of 137 studies (32 randomized controlled trials, 8577 participants; 65 cohort studies, 377 447 participants; and 40 pre–post studies, 11 295 participants) evaluated the comparative benefits of long-acting injectable versus oral antipsychotics for the treatment of schizophrenia (*11*). Data specific to aripiprazole were not reported separately. The primary outcome assessed was risk of hospitalization or relapse, which was found to be significantly lower for long-acting injectable antipsychotics compared with oral antipsychotics in each study design group: risk ratio (RR) 0.88, 95% confidence interval (CI) 0.79 to 0.99 (29 randomized controlled trials, 7833 participants); RR 0.92, 95% CI 0.88 to 0.98 (44 cohort studies, 106 136 participants); and RR 0.44, 95% CI 0.39 to 0.51 (28 pre–post studies, 17 876 participants).

A 2022 systematic review and network meta-analysis of 92 randomized controlled trials (22 645 participants) compared long-acting injectable with oral antipsychotics for relapse prevention in schizophrenia-spectrum disorders (*12*). For the primary efficacy outcome of relapse prevention, there was high confidence that aripiprazole (relative risk (RR) 0.35, 95% CI 0.22 to 0.49) and olanzapine (RR 0.35, 95% CI 0.23 to 0.54) long-acting injections were significantly more effective than placebo. There was also moderate confidence that paliperidone 3-monthly and once-monthly long-acting injections were significantly more effective than placebo: RR 0.24 (95% CI 0.13 to 0.42) and RR 0.36 (95% CI 0.24 to 0.53), respectively. There was low confidence that risperidone long-acting injection was significantly more effective than placebo for relapse prevention (RR 0.35, 95% CI 0.25 to 0.50). In head-to-head comparisons, no significant differences were seen between aripiprazole long-acting injection and other antipsychotics. For the outcome of tolerability (i.e. the proportion of participants who discontinued the trial due to adverse events), only oral olanzapine was

associated with a significant benefit compared with placebo (RR 0.61, 95% CI 0.41 to 0.90; low confidence in the evidence).

A 2021 systematic review and network meta-analysis of 78 randomized controlled trials (11 505 participants) compared different long-acting injectable antipsychotics for relapse prevention and acceptability in maintenance treatment of adults with non-affective psychoses (*13*). Primary outcomes were the proportion of patients who experienced at least one relapse and the proportion of patients who dropped out of trials for any reason (acceptability). The primary analysis found that most long-acting injectable antipsychotics evaluated were significantly more effective than placebo for relapse prevention, including aripiprazole (RR 0.29, 95% CI 0.21 to 0.39; moderate-certainty evidence), and others currently included on the EML. Paliperidone 3-monthly, aripiprazole and flupenthixol ranked best according to the mean surface under the cumulative ranking curve (SUCRA), with scores of 80.2%, 78.0% and 65.4%, respectively. In head-to-head comparisons, aripiprazole was significantly more effective at preventing relapse than haloperidol (RR 0.51, 95% CI 0.28 to 0.93). However, significant differences between aripiprazole and other second-generation antipsychotics were not reported: RR 0.74 (95% CI 0.51 to 1.08) versus paliperidone once-monthly and RR 0.83 (95% CI 0.54 to 1.27) versus risperidone. For the outcome of acceptability, most long-acting injectable antipsychotics evaluated were significantly more effective than placebo including aripiprazole (RR 0.49, 95% CI 0.41 to 0.58; moderate-certainty evidence) and others currently included on the EML. Zuclopenthixol, aripiprazole and perphenazine ranked best according to SUCRA with scores of 89.6%, 86.1% and 79.2%, respectively. In head-to-head comparisons, aripiprazole was significantly more acceptable than bromperidol, fluphenazine, paliperidone 3-monthly, pipothiazine and risperidone.

Randomized trials

The application also presented brief overviews of the findings of individual company-funded randomized trials that compared aripiprazole once-monthly with placebo and other antipsychotics (*14*–*20*).

Real-world studies

An online survey of 500 psychiatrists in Australia, Canada, France, Italy, Spain and the United Kingdom gathered real-world evidence of functional improvements with long-acting injectable antipsychotic treatment in recent-onset schizophrenia (*21*). Data were collected for 1000 patients receiving aripiprazole once monthly 400 mg and 1000 patients receiving paliperidone once monthly. Global assessment of functioning scores increased from baseline by 19.7 points and 16.3 points in patients treated with aripiprazole and paliperidone, respectively. Personal and social performance ratings of treatment

(deficits in self-care and disturbing and aggressive behaviours) were generally mild or borderline moderate for both groups.

A 2020 pharmaceutical-company-funded, retrospective, observational cohort study in Japan evaluated treatment persistence with aripiprazole once monthly versus oral aripiprazole (*22*). Patients receiving aripiprazole once monthly injection were significantly less likely to discontinue treatment than those in the total oral aripiprazole group (adjusted hazard ratio (HR) 0.54, 95% CI 0.53 to 0.86), and those with at least two prescription records of oral aripiprazole (adjusted HR 0.67, 95% CI 0.53 to 0.86). Other subgroup analyses had similar findings.

Summary of evidence: harms

A 52-week, company-funded, open-label study assessed the long-term safety and tolerability of aripiprazole once monthly injection 400 mg for the maintenance of schizophrenia (*17*). Patients were either previously enrolled in one of two randomized controlled trials of aripiprazole once monthly ($n = 984$) or new patients ($n = 194$). The study included an oral conversion phase, an oral stabilization phase and an open-label maintenance phase. During the maintenance phase, 934/1081 (86.4%) patients received aripiprazole 400mg for ≥ 6 months and 826/1081 (76.4%) patients received treatment for ≥ 12 months. Most patients (990/1081, 91.6%) started treatment at the 400 mg dose and maintained this dose. About two thirds of patients experienced treatment-emergent adverse effects; most were mild or moderate in severity. The most commonly reported treatment-emergent adverse effects were any extrapyramidal symptoms (9.0%), headache (7.6%) and nasopharyngitis (7.0%). Serious and severe treatment-emergent adverse effects were reported in 8.8% and 7.3% of patients, respectively. Treatment-emergent adverse effects led to study discontinuation in 6.3% of patients. Treatment-emergent adverse effects that occurred in ≥ 1% of patients and were classified as serious, severe or leading to study discontinuation included psychotic disorder and schizophrenia (serious: 1.4% and 1.9%, respectively; severe: 1.2% and 1.3%, respectively; leading to study discontinuation: 1.3% and 1.7%, respectively). No clinically relevant mean changes from baseline were seen in serum chemistry, haematology, urinalysis, insulin, fasting insulin, vital signs (including blood pressure, heart rate, body temperature, waist circumference and body mass index) or electrocardiogram parameters during the aripiprazole once monthly maintenance phase. A moderately higher incidence of potentially clinically relevant weight gain or loss (≥ 7% change from baseline) was seen at the last visit in new patients compared with patients who were enrolled from the randomized controlled trials. At the last visit of the maintenance phase, potentially clinically relevant prolactin concentrations (above the upper limit of normal) were reported in 2.1% of all patients. Extrapyramidal symptom rating scale scores remained stable throughout the maintenance phase.

In the 2022 network meta-analysis comparing the effectiveness and tolerability of oral and long-acting injectable antipsychotics, common antipsychotic-related adverse events were assessed as a secondary tolerability outcome (*12*). Compared with placebo: risperidone long-acting injection, oral paliperidone, oral lurasidone and oral risperidone were associated with a significantly higher risk of sedation; oral aripiprazole, olanzapine long-acting injection, oral olanzapine and paliperidone long-acting injection (1-monthly and 3-monthly) were associated with a significantly higher risk of weight gain; oral haloperidol, fluphenazine long-acting injection and pipothiazine long-acting injection were associated with a significantly higher risk of extrapyramidal symptoms; oral haloperidol, haloperidol long-acting injection and oral trifluoperazine were associated with a significantly higher risk of akathisia; oral olanzapine, olanzapine long-acting injection, paliperidone long-acting injection (1-monthly and 3-monthly), risperidone long-acting injection, oral risperidone and oral paliperidone-overall survival were associated with a significantly higher risk of hyperprolactinaemia; and oral olanzapine, olanzapine long-acting injection, oral asenapine, paliperidone long-acting injection (3-monthly) and oral risperidone were associated with a significantly lower risk of insomnia. No antipsychotics showed a higher risk of QTc prolongation and tardive dyskinesia as compared to placebo, although CIs were imprecise for most comparisons.

Additional evidence

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WHO guidelines

The 2023 WHO mhGAP guideline for mental, neurological and substance use disorders includes a conditional recommendation that long-acting injection antipsychotic medicines (fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol) should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects and individual preference (moderate-certainty evidence) (*23*). The WHO guideline also includes a strong recommendation that adults with a psychotic disorder (including schizophrenia) be offered oral antipsychotic medicines (namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine and risperidone), carefully balancing effectiveness, side-effects and individual patient preferences (moderate-certainty evidence).

Various national and professional society guidelines recommend offering long-acting injectable antipsychotic medicines to individuals with schizophrenia who need long-term treatment, request such treatments or who have difficulties adhering to medication.

Costs/cost–effectiveness

Data from the United States in 2019 indicate that schizophrenia was associated with an economic burden of 343.2 billion United States dollars (*24*). Schizophrenia also poses a high economic burden in low- and middle-income countries. Indirect costs are reported to account for 50–90% of the economic burden of schizophrenia (*25*). The direct costs of schizophrenia include inpatient/outpatient care, drug costs, treating and managing side-effects and comorbidities, rehabilitation, and social welfare administration. The indirect costs of schizophrenia include unemployment, reduced productivity at work, premature mortality, inability to live independently and financial impacts on family life (*25*–*27*).

The economic impact of aripiprazole once-monthly was evaluated in various studies that evaluated the effect on hospitalization rate versus oral antipsychotic therapy (*28*, *29*), comparative 6-month costs and outcomes versus paliperidone once-monthly (*30*) and cost–effectiveness versus paliperidone once-monthly in the treatment of schizophrenia (*31*). These studies were all conducted in the United States. They found significant reductions in total psychiatric hospitalization rates and cost-of-care savings for health plans (as a result of reduced psychiatric hospitalizations) with aripiprazole once-monthly, and economic dominance of aripiprazole once-monthly over paliperidone once monthly.

A 2023 analysis modelled the cost–effectiveness of aripiprazole once monthly versus paliperidone once-monthly in the treatment of stable schizophrenia from a societal perspective in Thailand over a lifetime horizon (*32*). The resultant incremental cost–effectiveness ratios were similar for each treatment: 81 652.85 Thai baht/QALY gained and 81 330.94 Thai baht/QALY gained for aripiprazole and paliperidone, respectively. The authors noted that if the cost of aripiprazole once-monthly decreased by 2%, it would become the dominant strategy.

The application reported list prices for aripiprazole once-monthly 400 mg prefilled syringe or vial ranging from 106 euros (€) in Indonesia to €420 in Germany. The application stated that following patent expiration in October 2024, generic alternatives may enter the market and lead to price reductions.

Comparative costs of other long-acting injectable antipsychotic medicines were not reported.

Availability

The application reported that aripiprazole once-monthly injection (300 mg and 400 mg) has regulatory approval in 62 (primarily high-income) countries/territories globally, with market availability in 58 of them. Patent expiry is reported in October 2024. Generic formulations are not currently available.

Other considerations

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Committee recommendations

The Expert Committee acknowledged that schizophrenia is a complex debilitating psychiatric disorder. It has one of the highest mortality risks of all mental health disorders and negatively affects several aspects of life.

The Committee noted that paliperidone once-monthly long-acting injection was currently included on the EML for maintenance treatment of schizophrenia. Listing is with a square box specifying risperidone long-acting injection as a therapeutic alternative. The Committee also noted that use of long-acting injectable antipsychotics required patients to be first stabilized on oral treatment before switching to the injectable preparation. Oral second-generation antipsychotics currently included on the EML for treatment of schizophrenia are risperidone as the class representative, with aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives. The Committee recognised the potential for continuity between oral aripiprazole and long-acting injectable aripiprazole.

The Committee noted from the most recent network meta-analysis presented in the application that long-acting injectable antipsychotics were more effective than placebo in preventing relapse. In head-to-head comparisons, the study found no significant differences between aripiprazole long-acting injection and other long-acting injectable antipsychotics medicines. However, direct heat-to-head trials comparing aripiprazole with other long-acting injectable antipsychotics were lacking.

Compared with oral antipsychotics, the Committee noted that data suggest long-acting injectable antipsychotics may offer benefit in terms of reduced risk of hospitalization or relapse, and better treatment adherence.

As regards harms, the Committee noted that the most commonly reported adverse effects of long-acting injectable antipsychotics were extrapyramidal symptoms. Compared with paliperidone or risperidone, aripiprazole has a lower risk of metabolic side-effects and weight gain.

The Committee recognized the substantially higher costs of long-acting antipsychotics compared with oral therapies but considered that the higher costs may be offset in part by reduced total cost of care for schizophrenia and fewer hospitalizations. There was limited information about the comparative costs of aripiprazole, paliperidone and risperidone long-acting injections. However, the Committee assumed that aripiprazole was likely to be more expensive than the others, since generics are available for paliperidone and risperidone, but not yet for aripiprazole.

The Committee agreed with the comments made by Médecins Sans Frontières, that aripiprazole long-acting injection may be a preferred therapeutic alternative to paliperidone than risperidone long-acting injection in low- and middle-income countries and in humanitarian contexts. Unlike risperidone, which requires reconstitution, cold chain and refrigerated storage, and

administration every 2 weeks, aripiprazole long-acting injection is available in a prefilled syringe formulation which does not require reconstitution, can be stored at room temperature and is administered once per month.

Based on these considerations, the Expert Committee recommended the inclusion of aripiprazole once-monthly long-acting injection on the core list of the EML for the maintenance treatment of adults with schizophrenia based on acceptable evidence of similar efficacy and a potentially lower risk of metabolic adverse effects compared with other long-acting injectable antipsychotics currently included on the EML. Listing is recommended for aripiprazole as a therapeutic alternative under the square box listing for paliperidone once-monthly long-acting injection.

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24.2 Medicines used in mood disorders

24.2.1 Medicines used in depressive disorders

Brexpiprazole – addition – EML

Brexpiprazole	ATC code: N05AX16

Proposal

Addition of brexpiprazole to the EML for the adjunctive treatment of adults with major depressive disorder.

Applicant

Otsuka America Pharmaceuticals Inc., Princeton NJ, United States of America

WHO technical department

The Department of Mental Health, Brain Health and Substance Use reviewed and provided comments on the application. The technical department thought it was difficult to justify the inclusion of brexpiprazole on the EML at this time, based on the available evidence for clinical efficacy and harms, low availability in low- and middle-income countries, high cost and patent status.

EML/EMLc

EML

Section

24.2.1 Medicines for depressive disorders

Dose form(s) & strengths(s)

Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

Core/complementary

Not specified

Individual/square box listing

Individual

Background

Brexpiprazole has not previously been evaluated for addition to the EML.

Public health relevance

According to the 2021 Global Burden of Disease study, the global prevalence of major depressive disorder is 3%, affecting almost 230 million people. It was responsible for about 46 million disability-adjusted life years (DALYs), equivalent to 1.6% of global DALYs. The prevalence of major depressive disorders varies by WHO region and World Bank income level, with the highest rates observed in the American, European and the Eastern Mediterranean regions, and in high-income and low-income countries (*1*).

The overall mortality rate of depressive episodes (indicative of major depressive disorder) was 0.20 per 100 000 from 1999 to 2020 in the United States, with females generally showing higher mortality rates than men (0.25 per 100 000 versus 0.12 per 100 000) (*2*).

Summary of evidence: benefits

Systematic reviews

The application identified 11 systematic reviews and/or meta-analyses on the comparative effectiveness and safety of brexpiprazole versus other adjunct antipsychotics to antidepressant treatments in major depressive disorder (*3*–*13*). Those studies prioritized in the application are summarized in the following paragraphs.

A 2023 systematic review and network meta-analysis of 56 randomized controlled trials (11 448 participants) compared and ranked the efficacy and safety of four antipsychotics (aripiprazole, brexpiprazole, olanzapine and quetiapine) in the adjuvant treatment of major depressive disorder in adults (*3*). The studies were short term, ranging from 4 to 12 weeks duration. The quality of studies in the network meta-analysis was generally low. The primary efficacy outcome was the mean change in Montgomery–Asberg Depression Rating Scale (MADRS) total score from baseline to endpoint. A total of 23 studies were included in the primary efficacy analysis. Compared with placebo, all antipsychotics were significantly more effective: quetiapine, standardized mean difference (SMD) −0.40 (95% confidence interval (CI) −0.68 to −0.12); olanzapine, SMD −0.35 (95% CI −0.59 to −0.11); aripiprazole, SMD −0.28 (95% CI −0.47 to −0.09); and brexpiprazole, SMD −0.25 (95% CI −0.42 to −0.07). No significant differences were seen between the different antipsychotics. For the primary efficacy outcome, the surface under the cumulative ranking curve (SUCRA) rankings from highest to lowest were quetiapine, olanzapine, aripiprazole, brexpiprazole and placebo. All antipsychotics were associated with significantly greater response rates compared with placebo. Aripiprazole was associated with significantly greater response rates than olanzapine and quetiapine. No significant difference was seen in response rate between brexpiprazole and the other antipsychotics. The

SUCRA rankings for response rate from highest to lowest were aripiprazole, brexpiprazole, olanzapine, quetiapine and placebo.

A 2023 systematic review and meta-analysis of 45 randomized controlled trials (12 725 participants) evaluated the efficacy and safety of antipsychotics as monotherapy and adjunctive therapy for the treatment of adults with major depressive disorder (*4*). Thirty-two studies involved adjunctive antipsychotic therapy. The primary efficacy outcome was study-defined treatment response, mainly the percentage of patients with at least 50% improvement in depressive symptom scale scores from baseline. Pooled analysis found that, collectively, all antipsychotics were significantly superior to placebo plus antidepressant therapy for treatment response: relative risk (RR) 1.35 (95% CI 1.26 to 1.45); 28 randomized controlled trials, 7366 participants. Individually, ziprasidone (RR 1.80, 95% CI 1.07 to 3.04; two randomized controlled trials, 199 participants), risperidone (RR 1.59, 95% CI 1.19 to 2.14; two randomized controlled trials, 313 participants), aripiprazole (RR 1.54, 95% CI 1.35 to 1.76; eight randomized controlled trials, 2416 participants), brexpiprazole (RR 1.41, 95% CI 1.21 to 1.66; six randomized controlled trials, 2167 participants), cariprazine (RR 1.27, 95% CI 1.07 to 1.52; one randomized controlled trial, 808 participants) and quetiapine (RR 1.23, 95% CI 1.08 to 1.41; six randomized controlled trials, 1339 participants) were significantly superior to placebo plus antidepressant therapy.

A 2022 meta-analysis of 15 randomized controlled trials (6570 participants) evaluated the efficacy of adjunctive aripiprazole (eight randomized controlled trials, 2671 participants) and brexpiprazole (seven randomized controlled trials, 3899 participants) in adults with major depressive disorder (*5*). The primary outcome measure was remission rate, where remission was defined as a MADRS total score of ≤ 10 and a ≥ 50% reduction from baseline at the follow-up visit. Overall, the study found high-certainty evidence that antipsychotic therapy was associated with significant benefit compared with placebo for remission rate (odds ratio (OR) 1.55, 95% CI 1.32 to 1.84). Individually, both aripiprazole (OR 1.82, 95% CI 1.52 to 2.19) and brexpiprazole (OR 1.37, 95% CI 1.09 to 1.73) were associated with significantly better regression rates (high-certainty evidence). For the secondary outcome of response rate (at least 50% reduction in MADRS score), there was high-certainty evidence of significant benefit over placebo for antipsychotic therapy (OR 1.62, 95% CI .44 to 1.82), aripiprazole (OR 1.84, 95% CI 1.54 to 2.19) and brexpiprazole (OR 1.46, 95% CI 1.24 to 1.71). Significant benefits were also reported for change in MADRS score from baseline and change in clinical global impression of severity scores from baseline.

A 2021 systematic review and meta-analysis of 49 randomized controlled trials (10 031 participants) evaluated the efficacy and tolerability of adding second-generation antipsychotics, esketamine, or lithium as adjunctive treatment to antidepressant therapy for major depressive disorder in adults (*6*). The trials

were of up to 12 weeks in duration. From the results of the random-effects meta-analysis, efficacy of all adjunctive treatments was significantly superior to placebo: lithium (OR 2.22, 95% CI 1.44 to 3.43; 14 randomized controlled trials, 640 participants); intranasal esketamine (OR 1.94, 95% CI 1.52 to 2.46; seven randomized controlled trials, 1287 participants); and second-generation antipsychotics (OR 1.59, 95% CI 1.44 to 1.75; 28 randomized controlled trials, 8077 participants). Numbers needed to treat for response were five, seven and 11 for lithium, intranasal esketamine and second-generation antipsychotics, respectively. Among second-generation antipsychotics, numbers needed to treat ranged from six for risperidone to 16 for brexpiprazole.

Randomized trials

The application included details of four company-funded randomized studies conducted in the clinical development programme for brexpiprazole to evaluate efficacy and safety in the adjunctive treatment of major depressive disorder: Pyxis (*14*), Polaris (*15*), Sirius (*16*) and Delphinus (*17*). Only the Delphinus trial, prioritized in the application, is summarized below.

The Delphinus trial was a multicentre, randomized, double-blind, active-referenced, placebo-controlled study of the efficacy and safety of brexpiprazole (2–3 mg/day) as adjunctive treatment for major depressive disorder (*17*). Patients ($n = 2174$) with a major depressive episode after an inadequate response to previous antidepressant treatment entered an 8- or 10-week prospective treatment phase and received double-blind placebo adjunct to open-label antidepressant. Following the prospective phase, participants with an inadequate response ($n = 503$) continued the same antidepressant therapy and were randomized (2:2:1) to receive adjunctive brexpiprazole 2–3 mg/day ($n = 197$), placebo ($n = 206$) or extended-release quetiapine 150–300 mg/day ($n = 100$) for 6 weeks. The primary efficacy endpoint was the change in the MADRS total score from randomization to week 6. After 6 weeks, brexpiprazole was associated with a significantly greater change from baseline in MADRS total score compared with placebo (−6.0 versus −4.6; least squares mean difference (LSMD) −1.48, 95% CI −2.566 to −0.39). No significant difference was seen between quetiapine and placebo for this outcome (−4.9 versus −4.6; LSMD −0.30, 95% CI −1.63 to 1.04). For the secondary efficacy endpoint of change from randomization to week 6 in mean score in the Sheehan Disability Scale, no significant difference was seen between brexpiprazole and placebo (−1.0 versus −0.7; LSMD −0.23, 95% CI −0.52 to 0.07). Significant differences were observed between brexpiprazole and placebo for other secondary efficacy outcomes including on the Clinical Global Impressions – Severity scale and Sheehan Disability Scale social life and family life items. No significant differences were seen for MADRS response, MADRS remission and Sheehan Disability Scale work/studies item.

Summary of evidence: harms

Systematic reviews

From the 2023 systematic review and network meta-analysis of aripiprazole, brexpiprazole, olanzapine and quetiapine in the adjuvant treatment of major depressive disorder in adults (3), no significant differences were found between the four antipsychotics and placebo for acceptability (all cause discontinuation, 20 randomized controlled trials, 7524 participants). For tolerability (discontinuation due to adverse events, 20 randomized controlled trials, 6524 participants) compared with placebo, quetiapine (RR 0.24, 95% CI 0.11 to 0.53), olanzapine (RR 0.30, 95% CI 0.10 to 0.55), brexpiprazole (RR 0.37, 95% CI 0.18 to 0.75) and aripiprazole (RR 0.39, 95% CI 0.22 to 0.69) were significantly less well tolerated. No significant differences were seen between the individual antipsychotics for either safety outcome.

From the 2022 systematic review and meta-analysis of the efficacy and safety of antipsychotics as monotherapy and adjunctive therapy (4), adjunctive antipsychotic therapy was significantly less well tolerated than placebo with higher intolerability-related discontinuation compared with placebo (RR 2.39, 95% CI 1.69 to 3.38; 26 randomized controlled trials, 7553 participants). Among individual antipsychotics, ziprasidone (RR 18.2, 95% CI 2.53 to 131; two randomized controlled trials, 200 participants), quetiapine (RR 4.19, 95% CI 2.22 to 7.90; five randomized controlled trials, 1326 participants), cariprazine (RR 3.30, 95% CI 1.59 to 6.84; one randomized controlled trial, 819 participants), brexpiprazole (RR 3.24, 95% CI 1.54 to 6.79; six randomized controlled trials, 2246 participants) and aripiprazole (RR 2.08, 95% CI 1.23 to 3.51; seven randomized controlled trials, 2308 participants) were associated with significantly higher discontinuation due to intolerability.

From the 2022 meta-analysis of adjunctive aripiprazole and brexpiprazole (5), the pooled ORs for any adverse events compared to placebo were 1.58 (95% CI 1.37 to 1.83) for antipsychotics, 1.37 (95% CI 1.21 to 1.56) for brexpiprazole and 1.95 (95% CI 1.52 to 2.51) for aripiprazole. For serious adverse events, the pooled ORs compared to placebo were not statistically significant for antipsychotics (OR 0.72, 95% CI 0.48 to 1.08), brexpiprazole (OR 0.65, 95% CI 0.40 to 1.05), or aripiprazole (OR 0.94, 95% CI 0.43 to 0.03). The most commonly reported serious adverse events were arterial occlusive disease, cellulitis and suicidal ideation.

From the 2021 systematic review and meta-analysis of adding the adjunctive second-generation antipsychotics, esketamine or lithium (6), the numbers needed to harm were nine, five and five for lithium, intranasal esketamine and second-generation antipsychotics, respectively. Among individual antipsychotics, the number needed to harm ranged from 19 with brexpiprazole to three with quetiapine.

Randomized trials

In the Delphinus trial (*17*), the most frequently reported treatment-emergent adverse events occurring in ≥ 5% of patients receiving brexpiprazole were akathisia (6.1%), somnolence (5.6%), headache (5.6%), increased appetite (2.5%) and dry mouth (1.0%). Body weight increase ≥ 7% at any post-baseline visit was reported by 5.7%, 5.1% and 2.4% in the brexpiprazole, aripiprazole and placebo groups, respectively. No consistent differences were observed between treatment groups for electrocardiogram assessment, vital signs and laboratory measurements.

Non-randomized studies

The company-funded Orion study was a 52-week (amended to 26-week), multicentre, open-label study to assess long-term safety and tolerability of brexpiprazole (0.5–3 mg/day) as adjunctive therapy to antidepressant treatment in adults with major depressive disorder (*18*). Of 2944 enrolled participants, 1895 (64.4%) completed the study. Almost three quarters of participants had at least 6 months exposure to brexpiprazole. A total of 2123/2938 (72.3%) participants experienced at least one treatment-emergent adverse event. The most frequently reported such events, occurring in ≥ 5% of participants, were weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%) and insomnia (6.3%). Severe treatment-emergent adverse events were experienced by 215/2938 (7.3%) participants. Discontinuation due to treatment-emergent adverse events was reported in 253/2938 (8.6%) participants. Mean weight gain from baseline was 2.7 kg and 3.2 kg at weeks 26 and 52, respectively. The percentage of participants with weight increase ≥ 7% from baseline was 25.8%. During the open-label treatment phase, suicidal ideation and suicidal behaviour were reported in 5.5% and 0.2% of participants, respectively. Treatment-emergent suicidal ideation occurred in 0.4% of patients. Four deaths occurred during the study, of which two were suicides. One suicide death was considered by the investigator to be possibly related to adjunctive brexpiprazole treatment.

The company-funded Aquila study was a 26-week, multicentre, open-label study of the safety and tolerability of brexpiprazole (1–3 mg/day) as adjunctive therapy to antidepressant treatment in elderly patients (≥ 65 years) with major depressive disorder (*19*). Of 132 treated participants, 44 (33.3%) withdrew from the study, including 24 (18.2%) due to adverse events. At least one treatment-emergent adverse effect was experienced by 102 (77.3%) participants. The most frequently reported treatment-emergent adverse events occurring in ≥ 5% of patients were fatigue (15.2%), restlessness (12.9%), increased appetite (9.8%), akathisia (8.3%) and weight gain (8.3%). The treatment-emergent adverse events most frequently responsible for study withdrawal were fatigue, akathisia, tremor, anxiety and depression. With respect to weight gain, the mean change in body weight from baseline to week 26 was 0.9 kg. Weight gain of ≥ 7% from baseline

was reported in four participants. Small mean increases in prolactin levels were reported in some participants. One participant without suicidal ideation at baseline experienced treatment-emergent suicidal ideation. No deaths occurred during the open-label treatment period.

Additional evidence

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WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders does not currently include any recommendations on adjunctive therapy to antidepressants for major depressive disorder (*20*).

A number of national and professional society guidelines recommend the use of adjunctive antipsychotics in patients with major depressive disorder who do not respond, or have limited response to, antidepressant treatment (*21*–*27*).

Costs/cost–effectiveness

The application reported ranges of lowest list prices for brexpiprazole by tablet strength in high- income countries and low- and middle-income countries. The lowest price in high-income countries ranges from 0.82 United States dollars (US$) to US$ 6.17 per unit, while the lowest price in low- and middle-income countries ranges from US$ 0.89 to US$ 5.09 per unit. Comparative prices of other antipsychotic medicines were not presented.

A 2017 company-funded modelled economic analysis evaluated the cost–effectiveness of adjunctive brexpiprazole versus alternative adjunctive treatments and antidepressant monotherapy for major depressive disorder from a United States payer perspective over a 48-week time horizon (*28*). Brexpiprazole was associated with higher clinical response and remission rates after 6 weeks compared with alternative adjunctive antipsychotics and antidepressant monotherapy, as well as higher total costs per patient. Overall, despite higher total costs, medical care cost-savings were observed with the use of brexpiprazole compared with alternatives.

A 2019 company-funded retrospective study compared real-world health-care utilization and costs of brexpiprazole and extended-release quetiapine as adjunctive treatment in patients with major depressive disorder using data from IQVIA Real World Data– US Adjudicated Claims database between July 2014 and September 2016 (*29*). Resource use and health-care costs in the 6 months after the start of treatment were compared between non-matched populations and between propensity score-matched groups. Significant differences were found between brexpiprazole and quetiapine in the non-matched cohorts for the following variables: proportion of patients with all-cause hospital stay (6.6%

versus 12.5%); proportion of patients with emergency department visit for any reason (16.9% versus 27.5%); mean number of all-cause hospitalizations (0.10 versus 0.21) and number of emergency department visits (0.30 versus 0.55) per patient; mean number of all-cause physician office visits per patient (14.89 versus 12.57); and mean medical costs (US$ 6421 versus US$ 8545) and pharmacy costs (US$ 7401 versus US$ 4691) per patient. No significant difference was seen between treatments for mean total health-care costs per patient (US$ 13 821 versus US$ 13 235). Differences in these parameters between the matched cohorts were not statistically significantly different.

A 2018 study compared health-care use and costs in 1380 patients with major depressive disorder using data from IQVIA's PharMetrics Plus Adjudicated Claims database before and after starting adjunctive atypical antipsychotic treatment with aripiprazole, brexpiprazole, lurasidone or quetiapine between 1 October 2014 and 30 September 2015 (*30*). Starting adjunctive antipsychotic treatment reduced all-cause and major depressive disorder-related hospitalizations by 12.2% and 10.4%, respectively, compared with antidepressant monotherapy. Starting antipsychotic treatment was associated with significant decreases in mean hospital costs (US$ 6217 and US$ 1166 per patient) compared with antidepressant monotherapy. Mean all-cause medical costs were significantly reduced by US$ 4513 per patient. Pharmacy costs were significantly increased by US$ 4236 per patient, the majority of which was attributed to psychotropic drug use.

A 2023 study investigated the use of health-care resources and costs associated with use of atypical antipsychotics as first- versus later-line adjunctive treatment of major depressive disorder in 508 830 patients using data from the Merative MarketScan Commercial Database between 1 January 2014 and 30 June 2019 (*31*). Use of health-care resources was significantly higher in patients starting adjunctive antipsychotics as later-line treatment than those starting as first-line treatment, largely attributable to outpatient visits. Later-line initiation was also associated with significantly higher health-care costs per patient than first-line initiation for all-cause health-care costs (mean difference US$ 2441) and mental health-related health-care costs (mean difference US$ 1762).

Availability

Brexpiprazole has been approved by the United States Food and Drug Administration for use as adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults. It has not been approved by the European Medicines Agency for this indication.

The application reported that brexpiprazole has market availability in 67 countries globally. It has regulatory approval for adjunctive treatment of major depressive disorder in 29 countries globally.

Brexpiprazole is under patent protection until 2033. Generic brands of brexpiprazole are not currently available.

Other considerations

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Committee recommendations

The Expert Committee acknowledged the substantial global burden of major depressive disorder and noted that the EML did not currently include any medicines for adjunctive therapy to antidepressant treatments.

From the evidence presented in the application, the Committee noted that most studies were short-term and showed only modest incremental benefit for brexpiprazole compared with placebo, Furthermore, the Committee noted that other second-generation antipsychotics and lithium showed similar or superior gains. In terms of safety, brexpiprazole appears to be less well tolerated than many other second-generation antipsychotics.

Based on these considerations, the Expert Committee did not recommend the inclusion of brexpiprazole on the EML for adjunctive treatment of major depressive disorder. The Committee recommended that any future application for medicines for adjunctive treatment of major depressive disorder should present a comprehensive evaluation of the evidence for all relevant treatment options for this indication, in preference to an application that focuses on a single medicine.

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24.5 Medicines for disorders due to psychoactive substance use

24.5.2 Medicines for nicotine use disorders

Cytisine – addition – EML

Cytisine (INN: cytisinicline) **ATC code: N07BA04**

Proposal

Addition of cytisine to the core list of the EML for treatment of nicotine dependence as an aid to stopping smoking and tobacco use in adults 18 years and older.

Applicant

Raymond G. Boyle, Independent Researcher, Minneapolis, MN United States of America; Judith J. Prochaska, Stanford University, Stanford, CA, United States of America; Krzysztof Przewozniak, University of Southern California, Los Angeles, CA, United States of America; WHO Department of Health Promotion

WHO technical department

The Department of Health Promotion reviewed and provided comments on the application. The technical department supported the inclusion of cytisine on the EML, highlighting that inclusion would increase the choice of cessation options for tobacco users who want to quit. The department considered that the application was supported by high population needs, strong evidence on efficacy and safety, and comparative cost–effectiveness.

EML/EMLc

EML

Section

24.5.2 Medicines for nicotine use disorders

Dose form(s) & strengths(s)

Solid oral dosage form: 1.5 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Cytisine has not previously been evaluated for inclusion on the EML.

Three pharmacotherapies for tobacco cessation are currently on the EML: nicotine replacement therapy (patch, gum, lozenge and mouth spray), bupropion and varenicline.

The International Nonproprietary Name for cytisine is cytisinicline. The name cytisine is used throughout the application because it is more widely recognized globally. It is also the name used in the WHO guideline for tobacco cessation in adults.

Public health relevance

The public health relevance for tobacco cessation interventions is well established.

Tobacco use is a major risk factor for cardiovascular and respiratory diseases, more than 20 different types or subtypes of cancer and many other debilitating health conditions. In 2020, 22.3% of the world's population used tobacco: 36.7% of men and 7.8% of women. Most (80%) of the 1.3 billion tobacco users globally live in low- and middle-income countries. Annually, more than 8 million people die from tobacco use, with most tobacco-related deaths occurring in low- and middle-income countries. To address the tobacco epidemic, WHO Member States adopted the Framework Convention on Tobacco Control (FCTC) in 2003. Currently 182 countries are Parties to this treaty (*1*).

Over 60% of people who smoke say they want to quit (*2*). Less than 5% of unassisted quit attempts are sustained to 1 year (*3*). As most quit attempts are unsuccessful and relapse is a hallmark of addiction, people who smoke and want to quit need access to a variety of options including behavioural interventions and pharmacological treatments.

Summary of evidence: benefits

The application presented findings from a literature search to identify cumulative reports that evaluated randomized controlled trials of cytisine with placebo, comparisons with other smoking cessation medications, or studies that tested different doses for smoking cessation.

A 2024 systematic review and meta-analysis of 14 randomized controlled trials evaluated the effectiveness of cytisine for tobacco cessation, and the effects of dose and concomitant use of behavioural or other pharmacological interventions on cessation outcomes (*4*). For the comparison of cytisine versus placebo or no intervention, there was moderate-certainty evidence that cytisine was associated with increased abstinence rates (24.0% versus 17.4%; risk ratio (RR) 2.65, 95% confidence interval (CI):1.50 to 4.67; six randomized controlled trials, 5194 participants). For the comparison of cytisine versus nicotine replacement

therapy, there was moderate-certainty evidence that cytisine was associated with increased abstinence rates (21.2% versus 15.5%; RR 1.36, 95% CI 1.06 to 1.73; two randomized controlled trials, 1511 participants). For the comparison of cytisine versus varenicline, there was low-certainty evidence of no significant difference in abstinence rates at 6 months between treatment groups (11.9% versus 11.6%; RR 0.96, 95% CI 0.63 to 1.45; three randomized controlled trials, 2508 participants). For the comparison of 6 weeks versus 12 weeks of cytisine treatment, there was moderate-certainty evidence that participants who received a longer duration of treatment were significantly more likely to quit smoking compared to participants who received a shorter duration of treatment (22.9% versus 18.3%; RR 1.29, 95% CI 1.02 to 1.63; two randomized controlled trials, 1009 participants).

A 2023 Cochrane systematic review and meta-analysis of 75 randomized controlled trials (45 049 participants) evaluated the effectiveness of nicotine receptor partial agonists for smoking cessation (5). The review included eight randomized controlled trials (almost 9000 participants) involving cytisine. Of these studies, four compared cytisine with placebo, two were comparisons with varenicline, one was a comparison with nicotine replacement therapy, and one was a dosing variation study. The review found moderate-certainty evidence that cytisine helped more people quit smoking compared with placebo as measured by smoking abstinence at longest follow-up (RR 1.30, 95% CI 1.15 to 1.47; four randomized controlled trials, 4623 participants). For the comparison of cytisine versus varenicline, there was moderate-certainty evidence of no significant difference in abstinence rates between treatments (RR 0.83, 95% CI 0.66 to 1.05; two randomized controlled trials, 2131 participants). For the comparison of cytosine versus nicotine replacement therapy, there was low-certainty evidence of greater benefit of cytisine (RR 1.43, 95% CI 1.13 to 1.80; one randomized controlled trial 1310 participants).

A 2023 Cochrane systematic review and component network meta-analysis of 319 clinical trials (157 179 participants) evaluated the comparative benefits of established pharmacotherapies and e-cigarettes as smoking cessation interventions (6). Among pharmacotherapies, there was high-certainty evidence that: varenicline (odds ratio (OR) 2.23, 95% credible interval (CrI) 2.02 to 2.68; 67 randomized controlled trials, 16 430 participants); cytisine (OR 2.21, 95% CrI 1.66 to 2.97; seven randomized controlled trials, 3848 participants); nicotine patch (OR 1.37, 95% CrI 1.20 to 1.56; 105 randomized controlled trials, 37 319 participants); fast-acting nicotine replacement therapy (OR 1.41, 95% CrI 1.29 to 1.55; 120 randomized controlled trials, 31 756 participants); and bupropion (OR 1.43, 95% CrI 1.26 to 1.43; 71 randomized controlled trials, 14 759 participants) were associated with significantly greater likelihood of abstinence at 6 months compared with placebo.

Summary of evidence: harms

The most frequently reported adverse events associated with cytisine include gastrointestinal disturbances and sleep disorders (*7*).

From the 2024 systematic review and meta-analysis of cytisine for tobacco cessation, higher (but non-significant) rates of adverse events were seen between cytisine and placebo (RR 1.19, 95% CI 0.99 to 1.42; six randomized controlled trials, 4578 participants) and between cytisine and varenicline (RR 1.37, 95% CI 0.57 to 3.33; two randomized controlled trials, 1345 participants). Most adverse events were reported as mild (*4*).

The 2023 Cochrane systematic review of nicotine receptor partial agonists for smoking cessation assessed harms at the participant level. Analysis of non-serious adverse events found a slight increase in patients receiving cytisine versus placebo (RR 1.22, 95% CI 1.07 to 1.39; four randomized controlled trials, 4052 participants). In an analysis of serious adverse events, no significant difference was seen between cytisine and placebo (RR 1.04, 95% CI 0.78 to 1.37; three randomized controlled trials, 3781 participants). For the comparison of cytisine and varenicline, there was low-certainty evidence of a trend towards fewer serious adverse events with cytisine (RR 0.67, 95% CI 0.44 to 1.03; two randomized controlled trials, 2017 participants). For the comparison of cytisine and nicotine replacement therapy, no significant difference was seen in the rate of serious adverse events between treatment groups (RR 1.15, 95% CI 0.76 to 1.75). Study-related neuropsychiatric or cardiac serious adverse events were not reported (*5*).

From the 2023 Cochrane systematic review of established pharmacotherapies and e-cigarettes as smoking cessation interventions, there was low-certainty evidence of no significant difference in serious adverse events compared to placebo for varenicline, cytisine, single-form nicotine replacement therapy and combination nicotine replacement therapy.

Additional evidence

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WHO guidelines

The 2024 WHO guidelines for tobacco cessation include a strong recommendation for cytisine as a pharmacological treatment option for tobacco users who smoke and are interested in quitting (*8*). The certainty of evidence for cytisine was considered moderate based on several factors including the variability in dosing, the small number of countries that have approved the medicine and the absolute number of studies that have evaluated treatment in different sociodemographic groups. The guideline highlights the potential for implementation of cytisine based on large benefits, small harms and lower cost.

Costs/cost–effectiveness

Health technology assessment bodies in several markets have concluded that treatment with cytisine has an acceptable cost–benefit profile as evidenced by its reimbursement status in countries in a number of regions. However, it has been highlighted that smoking cessation treatments are more expensive than smoking in many settings, particularly in low- and middle-income countries (9).

A 2020 trial-based cost-utility analysis evaluated the cost–effectiveness of cytisine versus placebo in addition to brief behavioural support for smoking cessation in 2472 patients newly diagnosed with tuberculosis in hospitals in Bangladesh and Pakistan (*10*). Mean total costs were higher in the cytisine group, while mean quality-adjusted life years (QALYs) were lower over 6 months. Thus, cytisine was dominated by placebo and it was concluded not to be cost-effective.

A 2014 modelled cost–effectiveness analysis from the United Kingdom evaluated the cost–effectiveness of cytisine compared with varenicline for smoking cessation (*11*). The analysis was limited by the identification of only two trials and the absence of manufacturer cost data for cytisine. Cytisine was assumed to be less costly and more effective than varenicline (i.e. dominant).

A 2018 study estimated the cost–effectiveness from a health-care perspective of introducing national level changes to smoking cessation services in England and the Netherlands, namely introduction of cytisine, increasing brief physician advice, increasing behavioural support with quitting and all changes implemented together (*12*). Costs and QALYs generated by those changes over 2, 5, 10 years and a lifetime were compared with those of current practice in each country. The combined change of adding all three cessation services was dominant over all alternative changes in both countries and would generate an incremental net benefit of 11.47 euros (€) and €9.96 per smoker over 2 years and of €56.16 and €60.72 per smoker over a lifetime in the Netherlands and England, respectively.

The application presented a comparison of costs for 12 weeks of treatment with cytisine versus other smoking cessation therapies in selected European countries (Table 13).

Table 13
Twelve-week treatment cost of smoking cessation therapies in Europe

Treatment	Cost per person, €					
	Denmark	Italy	Portugal	Spain	Sweden	United Kingdom
Cytisine	200	99	100	112	95	135
NRT patch	310	256	230	216	239	215
NRT spray	608	504	570	570	665	760
Varenicline	313	340	156	279	166	139

€: euro; NRT: nicotine replacement therapy; United Kingdom: United Kingdom of Great Britain and Northern Ireland.

Availability

The application reported that cytisine currently has regulatory approval as either a prescription or over-the-counter product in 34 (mostly high-income) countries globally.

Other considerations

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Committee recommendations

The Expert Committee recognized the important public health relevance of effective interventions for tobacco cessation, given the significant public health burden associated with smoking and tobacco use globally. The Committee noted that the EML currently includes multiple pharmacological treatment options for tobacco cessation (nicotine replacement therapy, bupropion and varenicline). The Committee agreed that the availability of a variety of effective treatment options can be beneficial in terms of offering choice for individuals wishing to quit, recognizing that quit attempts are often unsuccessful or are not sustained in the long term. The Committee also recognized the value of having multiple options available in the context of shortages, such as that reported in recent years for varenicline.

The Committee considered that the evidence presented in the application from three recent systematic reviews, with comparisons versus placebo and versus active comparators, supported the benefits of cytisine as an effective intervention for tobacco cessation as measured by abstinence rates. No serious safety concerns were identified, with adverse events being generally mild and manageable. Overall, the Committee considered that the balance of benefits to harms for cytisine was favourable.

The Committee noted that cytisine has limited global availability, but in settings where it is available, treatment costs are reportedly lower than for nicotine replacement therapy and varenicline. The Committee also noted that in low- and middle-income settings, tobacco cessation treatments, including cytisine, have been reported to be more expensive than smoking, and where cytisine in particular was determined not to be cost-effective. However, the Committee noted that cytisine is likely to be the most affordable option among the alternatives included on the Model List, particularly for people who do not benefit from insurance coverage or subsidized health care. In high-income settings, it has been determined to be cost-effective. The Committee acknowledged that the first invitation to manufacturers of medicinal products for treatment of disorders caused by use of tobacco to submit an expression of interest for WHO prequalification was published in 2023. The invitation is currently limited to nicotine replacement therapy (gum and transdermal patches) but other medicinal products on the EML could be added to this invitation in the future. The Committee considered that WHO prequalification of cytisine, bupropion and varenicline could support greater access and availability of quality-assured tobacco cessation products.

The Committee welcomed the publication in 2024 of the WHO guidelines for tobacco cessation, in which cytisine has a strong recommendation based on moderate-certainty evidence as a pharmacological treatment option for tobacco users interested in quitting.

Based on these considerations, the Expert Committee recommended the addition of cytisine to the core list of the EML as a treatment option for tobacco and smoking cessation. The Committee stressed the importance of counselling and behavioural support, in addition to pharmacotherapy, as part of comprehensive tobacco and smoking cessation efforts.

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Section 27: Vitamins and minerals

Iodine capsules – deletion – EML and EMLc

Iodine **ATC code: H03CA**

Proposal

Deletion of iodine 190 mg capsules for the prevention of iodine deficiency from the EML and EMLc.

Applicant

Guerbet, Villepinte, France

The applicant is the product owner and has marketing authorization of Oriodol brand of iodine 190 mg capsules.

WHO technical department

The Department of Nutrition and Food safety reviewed the application and advised that it did not oppose the removal of iodine capsules from the Model Lists. The department advised that it was not aware of any countries implementing iodine supplementation with iodized oil capsules. Additionally, outreach to partners did not reveal any country implementing iodized oil capsules.

EML/EMLc

EML and EMLc

Section

27 Vitamins and minerals

Dose form(s) & strengths(s)

Capsule: 190 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Iodine capsules for use in the prevention of iodine deficiency have been included on the EML since 1989 and on the EMLc since 2007.

The Model Lists currently also include iodized oil for oral or injectable administration for this indication.

Public health relevance

Not applicable

Summary of evidence: benefits

Not applicable

Summary of evidence: harms

Not applicable

Additional evidence

Not applicable

WHO guidelines

A 2007 joint statement by WHO and UNICEF recommended iodine supplementation for increasing iodine intake if iodized salt was not accessible in specific situations. Iodine supplements could be administered on a daily or annual basis using an iodized oil preparation in doses ranging from 90 micrograms per day or 200 mg per year for children younger than 2 years to 250 micrograms per day or 400 mg per year for women of reproductive age, and pregnant and lactating women (*1*).

Costs/cost–effectiveness

Not applicable

Availability

The applicant advised that due to decreasing medical needs over the years and the lack of demand for their product for the past 5 years, Guerbet has started withdrawing the marketing authorizations worldwide. Since 2022, all marketing authorization in export countries was withdrawn and Guerbet has applied for withdrawal of the last marketing authorization in France.

Other considerations

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Committee recommendations

The Expert Committee noted that the primary strategy for elimination of iodine deficiency is universal salt iodization, but that implementation of salt iodization programmes may not be feasible in all settings. In this case, iodine supplementation or iodine-fortified foods may be required for susceptible patient groups such as pregnant and lactating women, women of child-bearing age, and young children.

The Committee noted that an oral liquid formulation of iodized oil remains listed on the Model Lists as a treatment option for use in the prevention and treatment of iodine deficiency in such settings.

The Committee noted that the applicant had withdrawn marketing authorizations for its product worldwide due to decreased medical need and a lack of demand. No other manufacturers were identified.

The Expert Committee therefore recommended the deletion of iodine capsules 190 mg for prevention of iodine deficiency from the EML and EMLc.

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Annex 1

WHO Model List of Essential Medicines – 24th List (2025)

Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings. Medicines on the complementary list are presented in italics.

Where the *[c]* symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol** (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square box listings are applicable to medicine selection for children. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia*.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.** * Piped nitrous oxide is a major source of atmospheric pollution from healthcare facilities. Point-of-care cylinders are the preferred delivery system over centrally-supplied (piped) delivery systems.
oxygen	**Inhalation** (medical gas).
sevoflurane	**Inhalation.**

1.1.2 *Injectable medicines*

ketamine	**Injection:** 10 mg/mL [c] ; 50 mg/mL (as hydrochloride) in vial.
☐ propofol Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed	**Injection:** 0.25%; 0.5% (hydrochloride). **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule in 8% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed	**Injection:** 0.5% [c] ; 1%; 2% (hydrochloride). **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule in 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000.

Complementary List

*ephedrine**	***Injection:** 30 mg/mL (hydrochloride) in 1 mL ampoule.* * *For use in spinal anaesthesia during delivery, to prevent hypotension.*

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 400 micrograms/mL [c]; 1 mg/mL (sulfate) in 1 mL ampoule or vial.
☐ midazolam Therapeutic alternatives to be reviewed	**Injection**: 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. **Oral liquid:** 2 mg/mL [c]. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 1 mg/mL [c]; 2 mg/mL [c]; 10 mg/mL (sulfate or hydrochloride) in 1 mL ampoule.

1.4 Medical gases

oxygen*	**Inhalation** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 100 mg/5 mL [c], 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol (acetaminophen)*	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL**, 250 mg/5 mL [c]. **The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 100 mg, 250 mg [c]. **Tablet:** 250 mg, 325 mg, 500 mg. **Tablet (dispersible):** 100 mg, 250 mg [c]. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*

2.2 Opioid analgesics

codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr * For the management of cancer pain
☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg; 30 mg; 60 mg; 100 mg; 200 mg (morphine sulfate). **Injection:** 1 mg/mL [c] ; 2 mg/mL [c] ; 10 mg/mL (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 5 mg/5mL [c] ; 10 mg/5 mL (morphine hydrochloride or morphine sulfate). **Solid oral dosage form (slow release):** 5 mg [c] ; 10 mg; 30 mg; 60 mg; 100 mg; 200 mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).

Complementary list

*methadone**	***Tablet:** 5 mg; 10 mg (hydrochloride)* ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride)* ***Concentrate for oral liquid:** 25 mg/5mL; 50 mg/5mL (hydrochloride).* * *For the management of cancer pain.*

2.3 Medicines for other common symptoms in palliative care

amitriptyline	**Oral liquid:** 25 mg/5 mL [c] . **Tablet:** 10 mg; 25 mg; 75 mg.
cyclizine [c]	**Injection:** 50 mg/mL (lactate). **Tablet:** 50 mg (hydrochloride).
dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL [c] ; 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg; 0.75 mg; 1.5 mg; 2 mg; 4 mg (as dexamethasone base).

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube. **Tablet (scored):** 2 mg [c]; 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 12.5 mg/5 mL [c]; 50 mg/5 mL.
fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
haloperidol	**Injection:** 5 mg/mL in 1 mL ampoule. **Oral liquid:** 2 mg/mL. **Solid oral dosage form:** 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	**Injection:** 20 mg/mL.
hyoscine hydrobromide [c]	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches:** 1 mg/72 hours.
lactulose [c]	**Oral liquid:** 3.3 to 3.4 g/5 mL.
loperamide	**Solid oral dosage form:** 2 mg.
metoclopramide	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL. **Solid oral form:** 10 mg (hydrochloride).
midazolam	**Injection*:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL, 3 mL vial. * May be used for buccal administration when solution for oromucosal administration is not available. **Oral liquid:** 2mg/mL [c]. **Solid oral dosage form:** 7.5 mg; 15 mg. **Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL prefilled syringe.
☐ ondansetron Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg/mL in 2 mL, 4 mL ampoule (as hydrochloride dihydrate). **Oral liquid:** 4 mg/5 mL (as hydrochloride dihydrate). **Solid oral dosage form:** 4 mg; 8 mg (as hydrochloride dihydrate).

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
senna	**Oral liquid:** 7.5 mg/5 mL.
3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL [c]; 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg; 0.75 mg; 1.5 mg; 2 mg; 4 mg (as dexamethasone base).
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine*	**Oral liquid:** 1 mg/mL.
Therapeutic alternatives: – cetirizine – fexofenadine	**Tablet:** 10 mg. **Tablet (chewable):** 5 mg [c]; 10 mg [c]. * There may be a role for sedating antihistamines for limited indications (EMLc).
☐ prednisolone	**Oral liquid:** 5 mg/mL [c].
Therapeutic alternatives: – prednisone	**Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Granules for oral suspension*:** 50 mg. * Alternative formulations of activated charcoal may be used if granules are not available.
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule.
atropine	**Injection:** 1 mg/mL (sulfate) in 1 mL ampoule or vial.
calcium gluconate	**Injection:** 100 mg/mL (10%) in 10 mL ampoule or vial.
methylthioninium chloride (methylene blue)	**Injection:** 10 mg/mL in 10 mL ampoule.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*	
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.
penicillamine	**Solid oral dosage form:** 250 mg.
potassium ferric hexacyano-ferrate(II) -2H_2O (Prussian blue)	**Powder for oral administration.**
sodium nitrite	**Injection:** 30 mg/mL in 10 mL ampoule.
sodium thiosulfate	**Injection:** 250 mg/mL in 50 mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/mL in 2 mL ampoule; 100 mg/mL in 3 mL ampoule.*
fomepizole	***Injection:*** *5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule or vial.*
sodium calcium edetate	***Injection:*** *200 mg/mL in 5 mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*
5. MEDICINES FOR NEUROLOGICAL DISORDERS	
5.1 Medicines for central nervous system disorders	
5.1.1 ***Antiseizure medicines***	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg; 400 mg.
diazepam	**Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. * For use as adjunctive therapy for treatment-resistant partial or generalized seizures.

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*	
levetiracetam	**Oral liquid:** 100 mg/mL. **Tablet:** 250 mg; 500 mg; 750 mg; 1000 mg.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
magnesium sulfate*	**Injection:** 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). * For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
midazolam	**Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe. **Injection*:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. * For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 30 mg/mL or 60 mg/mL [c]; 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg; 30 mg; 60 mg; 100 mg.
phenytoin	**Injection:** 50 mg/mL (phenytoin sodium). **Oral liquid:** 30 mg/5 mL (phenytoin). **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (phenytoin sodium). **Tablet (chewable):** 50 mg (phenytoin).
prednisolone [c]	**Oral liquid:** 1 mg/mL. **Tablet:** 1 mg; 5 mg; 10 mg.
valproic acid (sodium valproate)* * Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg.

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

Complementary List

ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
levetiracetam	***Concentrate solution for infusion:*** *100 mg/mL in 5 mL ampoule or vial.* ***Solution for infusion:*** *5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.*
*valproic acid (sodium valproate)**	***Injection:*** *100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*

* *Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*

5.1.2 *Medicines for multiple sclerosis*

Complementary List

cladribine	***Tablet:*** *10 mg.*
glatiramer acetate	***Injection (subcutaneous):*** *20 mg/mL; 40 mg/mL in pre-filled syringe.*
*rituximab**	***Injection (intravenous):*** *500 mg/50 mL in 50 mL vial.*

* *including quality-assured biosimilars*

5.1.3 *Medicines for parkinsonism*

☐ biperiden	**Injection:** 5 mg (lactate) in 1 mL ampoule.
Therapeutic alternatives: – trihexyphenidyl	**Tablet:** 2 mg (hydrochloride).
levodopa + ☐ carbidopa	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.
Therapeutic alternatives: – benserazide (for carbidopa)	

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

5.1.4 *Medicines for cerebral palsy*

Complementary List

baclofen	***Intrathecal injection:*** *500 micrograms/mL in ampoule.* ***Oral liquid:*** *10 mg/5 mL.* ***Tablet:*** *10 mg.*

5.1.5 *Medicines for headache disorders*

5.1.5.1 *Medicines for acute migraine attacks*

acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
☐ ibuprofen Therapeutic alternatives: – naproxen	**Oral liquid:** 100 mg/5 mL [c]. **Tablet:** 200 mg; 400 mg.
paracetamol (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL [c]. * The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 250 mg [c]. **Tablet:** 250 mg; 325 mg; 500 mg. **Tablet (dispersible):** 100 mg, 250 mg [c].
☐ sumatriptan Therapeutic alternatives: – eletriptan	**Tablet:** 50 mg.

5.1.5.2 *Medicines for migraine prophylaxis*

propranolol	**Tablet:** 10 mg [c]; 40 mg (hydrochloride).

5.1.5.3 *Medicines for cluster headache*

prednisolone	**Tablet:** 5 mg; 25 mg.
sumatriptan	**Injection (subcutaneous):** 6 mg/ 0.5 mL in pre-filled syringe or pen.
verapamil	**Tablet (immediate-release):** 40 mg; 80 mg; 120 mg. **Tablet (extended-release):** 120 mg; 180 mg; 240 mg.

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

5.1.6 *Medicines for central nervous system infections*

5.1.6.1 *Medicines for bacterial central nervous system infections*

amoxicillin

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c].

Solid oral dosage form: 250 mg; 500 mg (as trihydrate).

Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate) [c].

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	

ceftriaxone* [a]

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

chloramphenicol

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.

Powder for injection: 1 g (sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates* [c]	

Complementary List

*meropenem** [a]

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*

[a] > 3 months.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis in neonates* [c]

5.1.6.2 ***Medicines for viral central nervous system infections***

☐ aciclovir

Therapeutic alternatives:
– valaciclovir (oral)

Oral liquid: 200 mg/5 mL [c].

Powder for solution for infusion: 250 mg (as sodium dihydrate) in vial.

Solution for infusion: 25 mg/mL (as sodium) in vial.

Tablet: 200 mg.

5.2 Medicines for peripheral nervous system disorders

5.2.1 ***Medicines for Guillain-Barré syndrome***

Complementary List

normal immunoglobulin

Intravenous administration: *5%; 10% protein solution.*

5.2.2 ***Medicines for myasthenia gravis***

neostigmine

Injection: 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.

Tablet: 15 mg (bromide).

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

Complementary List

pyridostigmine	***Injection:*** *5 mg/mL (bromide) in ampoule or vial.* ***Tablet (scored):*** *60 mg (bromide).*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

albendazole	**Tablet (chewable, scored):** 400 mg.
ivermectin	**Tablet:** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 500 mg. **Tablet (scored):** 600 mg.
pyrantel	**Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 *Antifilarials*

albendazole	**Tablet (chewable, scored):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
☐ ivermectin	**Tablet:** 3 mg.

Therapeutic alternatives:
- moxidectin

6.1.3 *Antischistosomals and other antitrematode medicines*

☐ praziquantel*	**Tablet:** 150 mg, 500 mg. **Tablet (scored):** 600 mg.

Therapeutic alternatives:
- arpraziquantel (Tablet (dispersible): 150 mg) [c].

* The square box applies only to the listing of praziquantel on the EMLc for schistosomiasis

triclabendazole	**Tablet (scored):** 250 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* * *For use when praziquantel treatment fails.*
6.1.4 ***Cysticidal medicines***	
Complementary List	
albendazole	***Tablet (chewable):*** *200 mg* **[c]** *.* ***Tablet (chewable, scored):*** *400 mg.*
mebendazole	***Tablet (chewable)****: 100 mg* **[c]** *, 500 mg.*
praziquantel	***Tablet:*** *150 mg; 500 mg.* ***Tablet (scored)****: 600 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programmes involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 *Access group antibiotics*

amikacin

Injection: 50 mg/mL (as sulfate) [c]; 250 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *High-risk febrile neutropenia* – *Pyelonephritis or prostatitis (severe)*	– *Sepsis in neonates and children* [c]

amoxicillin

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c].

Solid oral dosage form: 250 mg; 500 mg; 1g (as trihydrate).

Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate) [c].

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* [c] – *Complicated severe acute malnutrition* [c] – *Exacerbations of COPD* – *Otitis media* – *Pharyngitis* – *Progressive apical dental abscess* – *Sepsis in neonates and children* [c] – *Sinusitis* – *Uncomplicated severe acute malnutrition* [c]	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid

Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.

Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c].

Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt).

Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt) [c]; 250 mg (as trihydrate) + 62.5 mg (as potassium salt) [c].

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections (mild to moderate)* – *Exacerbations of COPD* – *Hospital acquired pneumonia* – *Low-risk febrile neutropenia* – *Lower urinary tract infections* – *Sinusitis* – *Skin and soft tissue infections*	– *Bone and joint infections* – *Community-acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* – *Otitis media* – *Surgical prophylaxis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections* [c] – *Complicated severe acute malnutrition* [c] – *Sepsis in neonates and children* [c]	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin

Powder for injection: 1.2 million IU (≈ 900 mg) in vial [c] ; 2.4 million IU (≈ 1.8 g) in vial.

FIRST CHOICE	SECOND CHOICE
- *Syphilis*	

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
- *Community acquired pneumonia (severe)* [c] - *Complicated severe acute malnutrition* [c] - *Sepsis in neonates and children* [c] - *Syphilis*	- *Acute bacterial meningitis*

cefalexin

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous).

Solid oral dosage form: 250 mg; 500 mg (as monohydrate).

Tablet (dispersible): 125 mg [c] ; 250 mg [c] .

FIRST CHOICE	SECOND CHOICE
- *Skin and soft tissue infections*	- *Exacerbations of COPD* - *Pharyngitis*

cefazolin [a]

Powder for injection: 1 g (as sodium salt) in vial.

[a] > 1 month.

FIRST CHOICE	SECOND CHOICE
- *Surgical prophylaxis*	- *Bone and joint infections*

chloramphenicol

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults.

Powder for injection: 1 g (as sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	- *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate).

Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride) [c].

FIRST CHOICE	SECOND CHOICE
– *Necrotizing fasciitis*	– *Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:

– 4th level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 250 mg [c], 500 mg; 1 g (as sodium).

Powder for injection: 250 mg [c], 500 mg (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL, 250 mg/5 mL (as sodium) [c].

* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– *Bone and joint infections* – *Skin and soft tissue infections*	– *Sepsis in neonates and children* [c]

doxycycline [a]

Oral liquid: 50 mg/5 mL (calcium) [c].

Powder for oral liquid: 25 mg/5 mL (monohydrate) [c].

Powder for injection: 100 mg in vial.

Solid oral dosage form: 50 mg [c]; 100 mg (as hyclate).

Tablet (dispersible): 100 mg (as monohydrate) [c].

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
– *Cholera* – *Sexually transmitted infection due to Chlamydia trachomatis*	– *Cholera* [c] – *Community acquired pneumonia (mild to moderate)* – *Exacerbations of COPD*

6. ANTI-INFECTIVE MEDICINES *(continued)*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates* [c] – *Community acquired pneumonia (severe)* [c] – *Complicated intraabdominal infections* [c] – *Complicated severe acute malnutrition* [c] – *Sepsis in neonates and children* [c]	– *Gonorrhoea* – *Surgical prophylaxis*

metronidazole

Injection: 500 mg in 100 mL vial.

Oral liquid: 200 mg/5 mL (as benzoate).

Suppository: 500 mg; 1 g.

Tablet: 200 mg; 250 mg; 400 mg; 500 mg.

FIRST CHOICE	SECOND CHOICE
– *C. difficile infection* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Necrotizing fasciitis* – *Surgical prophylaxis* – *Trichomoniasis*	– *Complicated intraabdominal infections (mild to moderate)*

nitrofurantoin

Oral liquid: 25 mg/5 mL [c].

Solid oral dosage form: 50 mg [c]; 100 mg.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

phenoxymethylpenicillin

Powder for oral liquid: 250 mg/5 mL (as potassium).

Solid oral dosage form: 250 mg; 500 mg (as potassium).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)* – *Pharyngitis* – *Progressive apical dental abscess*	

procaine benzylpenicillin*

Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial.

* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

FIRST CHOICE	SECOND CHOICE
– *Syphilis (congenital)* [c]	– *Syphilis*

spectinomycin

Powder for injection: 2 g (as hydrochloride) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Gonorrhoea*

sulfamethoxazole + trimethoprim

Injection: 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.

Oral liquid: 200 mg + 40 mg/5 mL.

Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.

Tablet (dispersible): 100 mg + 20 mg [c] .

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	– *Acute invasive bacterial diarrhoea / dysentery*

trimethoprim

Tablet: 100 mg; 200 mg.

Oral liquid: 50 mg/5 mL [c] .

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 ***Watch group antibiotics***

azithromycin

Solid oral dosage form: 250 mg; 500 mg (anhydrous).
Powder for oral liquid: 200 mg/5 mL (anhydrous) [c] .

FIRST CHOICE	SECOND CHOICE
– *Cholera* – *Enteric fever* – *Gonorrhoea* – *Sexually transmitted infection due to Chlamydia trachomatis* – *Trachoma* – *Yaws*	– *Acute invasive bacterial diarrhoea / dysentery* – *Gonorrhoea*

cefixime

Powder for oral liquid: 100 mg/5 mL [c] .
Solid oral dosage form: 200 mg; 400 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute invasive bacterial diarrhoea / dysentery* – *Gonorrhoea*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intraabdominal infections (severe)* – *Hospital acquired pneumonia* – *Pyelonephritis or prostatitis (severe)*	– *Bone and joint infections* – *Pyelonephritis or prostatitis (mild to moderate)* – *Sepsis in neonates and children* [c]

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Endophthalmitis* – *Enteric fever* – *Gonorrhoea* – *Hospital acquired pneumonia* – *Necrotizing fasciitis* – *Pyelonephritis or prostatitis (severe)*	– *Acute invasive bacterial diarrhoea / dysentery* – *Bone and joint infections* – *Pyelonephritis or prostatitis (mild to moderate)* – *Sepsis in neonates and children* [c]

cefuroxime

Powder for injection: 250 mg; 750 mg; 1.5 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Surgical prophylaxis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

ciprofloxacin

Oral liquid: 250 mg/5 mL (anhydrous) [c].

Solution for IV infusion: 2 mg/mL (as hyclate) [c].

Solid oral dosage form: 100 mg [c]; 250 mg; 500 mg (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Acute invasive bacterial diarrhoea / dysentery* – *Enteric fever* – *Low-risk febrile neutropenia* – *Pyelonephritis or prostatitis (mild to moderate)*	– *Cholera* – *Complicated intraabdominal infections (mild to moderate)*

☐ clarithromycin †

Therapeutic alternatives:

– erythromycin*

* as second choice treatment for pharyngitis in children (EMLc only)

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL.

Powder for injection: 500 mg in vial.

Solid oral dosage form: 250 mg [c]; 500 mg.

† clarithromycin is also listed for use in combination regimens for eradication of *H. pylori* in adults.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)*	– *Pharyngitis*

piperacillin + tazobactam

Powder for injection: 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia* – *Hospital acquired pneumonia* – *Necrotizing fasciitis*	

vancomycin*

Capsule: 125 mg; 250 mg (as hydrochloride).

* vancomycin powder for injection may also be used for oral administration

FIRST CHOICE	SECOND CHOICE
	– *C. difficile infection*

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

ceftazidime	***Powder for injection:*** *250 mg; 1 g (as pentahydrate) in vial.*
	FIRST CHOICE *– Endophthalmitis* | **SECOND CHOICE**
☐ *meropenem** [a] *Therapeutic alternatives*:* *– imipenem + cilastatin* ** complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*	***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.* [a] > 3 months.
	FIRST CHOICE | **SECOND CHOICE** *– Acute bacterial meningitis in neonates* [c] *– Complicated intraabdominal infections (severe)* *– High-risk febrile neutropenia*
vancomycin	***Powder for injection:*** *250 mg; 500 mg; 1 g (as hydrochloride) in vial.*
	FIRST CHOICE *– Endophthalmitis* *– Necrotizing fasciitis* | **SECOND CHOICE** *– High-risk febrile neutropenia*

6.2.3 *Reserve group antibiotics*

Complementary List

cefiderocol	***Powder for injection:*** *1 g (as sulfate tosylate) in vial.*
ceftazidime + avibactam	***Powder for injection:*** *2 g + 0.5 g in vial.*
ceftolozane + tazobactam	***Powder for injection:*** *1 g + 0.5 g in vial.*
colistin	***Powder for injection:*** *1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial.*
fosfomycin	***Powder for injection:*** *2 g; 4 g (as sodium) in vial.*
☐ *linezolid* *Therapeutic alternatives:* *– tedizolid phosphate*	***Injection for intravenous administration:*** *2 mg/mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet:*** *600 mg.* ***Tablet (dispersible):*** *150 mg* [c] .

6. ANTI-INFECTIVE MEDICINES *(continued)*

meropenem + vaborbactam	***Powder for injection:*** *1 g (as trihydrate) + 1 g in vial.*
plazomicin	***Injection:*** *500 mg/10 mL.*
polymyxin B	***Powder for injection:*** *500 000 IU (equivalent to 50 mg polymyxin B base) in vial.*

6.2.4 *Antileprosy medicines*

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Oral liquid:** 20 mg/mL [c]. **Solid oral dosage form:** 150 mg; 300 mg.

6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

amikacin	**Injection:** 250 mg/mL (as sulfate) in 2 mL vial.
amoxicillin + clavulanic acid*	**Powder for oral liquid:** 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt). **Tablet (dispersible):** 250 mg (as trihydrate) + 62.5 mg (as potassium salt) [c]. * For use only in combination with meropenem or imipenem+cilastatin.
bedaquiline	**Tablet:** 20 mg [c]; 100 mg.
clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
☐ cycloserine	**Solid oral dosage form:** 125 mg [c]; 250 mg.

Therapeutic alternatives:
– terizidone

6. ANTI-INFECTIVE MEDICINES *(continued)*	
delamanid	**Tablet (dispersible):** 25 mg [c]. **Tablet:** 50 mg.
ethambutol	**Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg [c].
ethambutol + isoniazid + pyrazinamide + rifampicin	**Tablet:** 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	**Tablet:** 275 mg + 75 mg + 150 mg.
☐ ethionamide Therapeutic alternatives*: – protionamide * for multidrug-resistant tuberculosis	**Tablet:** 250 mg. **Tablet (dispersible):** 125 mg [c].
isoniazid	**Tablet:** 100 mg; 300 mg. **Tablet (dispersible, scored):** 100 mg [c].
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg [c].
isoniazid + rifampicin	**Tablet:** 75 mg + 150 mg; 150 mg + 300 mg. **Tablet (dispersible):** 50 mg + 75 mg [c].
isoniazid + rifapentine	**Tablet (scored):** 300 mg + 300 mg.
levofloxacin	**Tablet:** 250mg; 500 mg; 750 mg. **Tablet (dispersible):** 100 mg [c].
linezolid	**Tablet:** 600 mg. **Tablet (dispersible):** 150 mg [c].
☐ meropenem Therapeutic alternatives: – imipenem + cilastatin	**Powder for injection:** 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
p-aminosalicylate sodium	**Powder for oral solution:** 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid).
pretomanid	**Tablet:** 200 mg.
pyrazinamide	**Tablet:** 400 mg; 500 mg **Tablet (dispersible):** 150 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
rifabutin	**Solid oral dosage form:** 150 mg.
rifampicin	**Oral liquid:** 20 mg/mL [c].
	Solid oral dosage form: 150 mg; 300 mg.
rifapentine	**Tablet:** 150 mg; 300 mg.
	Tablet (dispersible, scored): 150 mg [c].
streptomycin [c]	**Powder for injection:** 1 g (as sulfate) in vial.
6.3 Antifungal medicines	
amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial.
	Powder for injection: 50 mg (as sodium deoxycholate) in vial.
	* Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.
clotrimazole	**Vaginal cream:** 1%; 10%.
	Vaginal tablet: 100 mg; 500 mg.
fluconazole	**Capsule:** 50 mg.
	Injection: 2 mg/mL in vial.
	Oral liquid: 50 mg/5 mL.
	Powder for oral liquid: 50 mg/5 mL [c].
flucytosine	**Capsule:** 250 mg.
	Infusion: 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL [c].
	Solid oral dosage form: 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg.
	Oral liquid: 10 mg/mL.
	* For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 100 000 IU/mL [c]. **Pessary:** 100 000 IU. **Solid oral dosage form:** 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg **Powder for injection:** 200 mg in vial **Powder for oral liquid:** 40 mg/mL * For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.
Complementary List	
☐ *micafungin* *Therapeutic alternatives:* – *anidulafungin* – *caspofungin*	***Powder for injection:*** *50 mg (as sodium); 100 mg (as sodium) in vial.*
potassium iodide	***Saturated solution.***

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

☐ aciclovir	**Oral liquid:** 200 mg/5 mL [c].
Therapeutic alternatives: – valaciclovir (oral)	**Powder for solution for infusion:** 250 mg (as sodium dihydrate) in vial. **Solution for infusion:** 25 mg/mL (as sodium) in vial. **Tablet:** 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

abacavir	**Tablet:** 300 mg (as sulfate).
lamivudine	**Oral liquid:** 50 mg/5 mL [c]. **Tablet:** 150 mg.
tenofovir disoproxil fumarate†	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † also indicated for pre-exposure prophylaxis.
zidovudine	**Capsule:** 250 mg. **Oral liquid:** 50 mg/5 mL. **Solution for IV infusion:** 10 mg/mL in 20 mL vial. **Tablet:** 300 mg.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

efavirenz	**Tablet:** 600 mg.
nevirapine [a]	**Oral liquid:** 50 mg/5 mL. **Tablet (dispersible):** 50 mg; 200 mg. [a] > 6 weeks

6.4.2.3 *Protease inhibitors*

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir + ritonavir	**Tablet (heat stable):** 300 mg (as sulfate) + 100 mg.
darunavir [a]	**Tablet:** 75 mg; 400 mg; 600 mg; 800 mg [a] > 3 years
lopinavir + ritonavir	**Solid oral dosage form:** 40 mg + 10 mg [c]. **Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	**Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 *Integrase inhibitors*

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg [c]. [a] ≥ 4 weeks and ≥ 3 kg **Tablet:** 50 mg [a] ≥ 25 kg

6. ANTI-INFECTIVE MEDICINES *(continued)*

raltegravir*	**Granules for oral suspension:** 100 mg in sachet. **Tablet (chewable):** 25 mg. **Tablet:** 400 mg. * For use in pregnant women and in second-line regimens in accordance with WHO treatemnt guidelines.

6.4.2.5 ***Fixed-dose combinations of antiretroviral medicines***

abacavir + dolutegravir + lamivudine [c]	**Tablet (dispersible):** 60 mg (as sulfate) + 5 mg + 30 mg.
abacavir + lamivudine	**Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.
dolutegravir + lamivudine + tenofovir	**Tablet:** 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
efavirenz + ☐ emtricitabine + tenofovir Therapeutic alternatives: – lamivudine (for emtricitabine)	**Tablet:** 600 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).
efavirenz + lamivudine + tenofovir	**Tablet:** 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
☐ emtricitabine + tenofovir† Therapeutic alternatives: – lamivudine (for emtricitabine)	**Tablet:** 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † combination also indicated for pre-exposure prophylaxis
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg [c]; 150 mg + 300 mg.

6.4.2.6 ***Medicines for prevention of HIV-related opportunistic infections***

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6.4.3 ***Other antivirals***

valganciclovir*	**Tablet:** 450 mg (as hydrochloride). * For the treatment of cytomegalovirus retinitis (CMVr).

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary list

*oseltamivir**	***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).* ***Powder for oral liquid:*** *6 mg/mL (as phosphate)* **[c]** **.** * *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
*valganciclovir** **[c]**	***Powder for oral solution:*** *50 mg/mL (as hydrochloride).* ***Tablet:*** *450 mg (as hydrochloride).* * *For the treatment of cytomegalovirus retinitis (CMVr).*

6.4.4 Antihepatitis medicines

6.4.4.1 ***Medicines for hepatitis B***

6.4.4.1.1 ***Nucleoside/Nucleotide reverse transcriptase inhibitors***

entecavir	**Oral liquid:** 0.05 mg/mL **Tablet:** 0.5 mg; 1 mg
tenofovir disoproxil fumarate	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

6.4.4.2 ***Medicines for hepatitis C***

Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.

6.4.4.2.1 ☐ ***Pangenotypic direct-acting antiviral combinations***

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride). * Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg (as dihydrochloride) + 400 mg.
glecaprevir + pibrentasvir	**Granules:** 50 mg + 20 mg in sachet **[c]** **.** **Tablet:** 100 mg + 40 mg.
ravidasvir*	**Tablet:** 200 mg. * Pangenotypic when used in combination with sofosbuvir
sofosbuvir*	**Granules:** 200 mg in sachet **[c]** **.** **Tablet:** 200 mg; 400 mg. * Pangenotypic when used in combination with daclatasvir or ravidasvir
sofosbuvir + velpatasvir	**Granules:** 150 mg + 37.5 mg; 200 mg + 50 mg in sachet **[c]** **.** **Tablet:** 200 mg + 50 mg **[c]** ; 400 mg + 100 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4.2.2 ***Non-pangenotypic direct-acting antiviral combinations***

ledipasvir + sofosbuvir	**Tablet:** 90 mg + 400 mg.

6.4.4.2.3 ***Other antivirals for hepatitis C***

ribavirin*	**Injection for intravenous administration:** 800 mg; 1 g in 10 mL phosphate buffer solution. **Solid oral dosage form:** 200 mg; 400 mg; 600 mg. * For the treatment of hepatitis C, in combination with direct acting anti-viral medicines.

6.5 Antiprotozoal medicines

6.5.1 ***Antiamoebic and antigiardiasis medicines***

diloxanide* [a] * proposed for deletion in 2027	**Tablet:** 500 mg (furoate). [a] > 25 kg.
☐ metronidazole Therapeutic alternatives: – tinidazole	**Injection:** 500 mg in 100 mL vial. **Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg; 250 mg; 400 mg; 500 mg.

6.5.2 ***Antileishmaniasis medicines***

amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial. **Powder for injection:** 50 mg (as sodium deoxycholate) in vial. * Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.
meglumine antimoniate	**Injection:** 1.5 g/5 mL in 5 mL ampoule.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	**Injection:** 100 mg/mL in 30 mL vial.

6.5.3 ***Antimalarial medicines***

6.5.3.1 ***Medicines for curative treatment***

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to WHO treatment guidelines for malaria.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
artemether	**Oily injection:** 80 mg/mL in 1 mL ampoule. For use in the management of severe malaria.
artemether + lumefantrine	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg [c].
artesunate	**Powder for injection:** 30 mg; 60 mg; 120 mg in vial. For use in the management of severe malaria. **Rectal dosage form:** 100 mg [c] For pre-referral treatment of severe malaria only.
artesunate + amodiaquine	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.
artesunate + mefloquine	**Tablet:** 25 mg + 50 mg (as hydrochloride); 100 mg + 200 mg (as hydrochloride).
artesunate + pyronaridine	**Granules:** 20 mg + 60 mg (tetraphosphate) [c]. **Tablet:** 60 mg + 180 mg (tetraphosphate).
artesunate – sulfadoxine + pyrimethamine	**Co-packaged scored tablets:** artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	**Oral liquid:** 50 mg/5 mL (base). **Tablet:** 150 mg (base). For use only in the treatment of *Plasmodium vivax* infection.
dihydroartemisinin + piperaquine	**Tablet:** 20 mg + 160 mg (phosphate); 40 mg + 320 mg (phosphate); 60 mg + 480 mg (phosphate); 80 mg + 640 mg (phosphate). **Tablet (dispersible):** 20 mg + 160 mg (phosphate); 40 mg + 320 mg (phosphate) [c].
primaquine	**Tablet:** 7.5 mg; 15 mg (as phosphate). For use to reduce the transmission of *Plasmodium falciparum* and for radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections.
quinine	**Solution for infusion:** 60 mg/mL [c]; 300 mg/mL (hydrochloride) in 2 mL ampoule. For use in the management of severe malaria.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.3.2 ***Medicines for chemoprevention***

amodiaquine – sulfadoxine + pyrimethamine [c]	**Co-packaged dispersible tablets:** amodiaquine 75 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]. amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]. amodiaquine 150 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]. amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
sulfadoxine + pyrimethamine	**Tablet (dispersible):** 250 mg + 12.5 mg [c]; 500 mg + 25 mg.

6.5.3.3 ***Medicines for chemoprophylaxis in travellers***

chloroquine	**Oral liquid:** 50 mg/5 mL (base). **Tablet:** 150 mg (base). For use only for prophylaxis of *Plasmodium vivax* infection.
doxycycline [a]	**Oral liquid:** 50 mg/5 mL (calcium). **Powder for oral liquid:** 25 mg/5 mL (monohydrate). **Solid oral dosage form:** 50 mg; 100 mg (as hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). [a] > 8 years.
mefloquine [a]	**Tablet (scored):** 250 mg (as hydrochloride).

6.5.4 ***Antipneumocystosis and antitoxoplasmosis medicines***

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL [c]. **Tablet:** 100 mg + 20 mg [c]; 400 mg + 80 mg [c]; 800 mg + 160 mg **Tablet (dispersible):** 100 mg + 20 mg [c].

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

pentamidine	***Tablet:** 200 mg; 300 mg (as isethionate).*

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 *African trypanosomiasis*

fexinidazole*	**Tablet:** 600 mg * For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	**Powder for injection:** 300 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg/mL (hydrochloride) in 50 mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
melarsoprol	**Injection:** 180 mg/5 mL in 5 mL ampoule (3.6% solution).
nifurtimox*	**Tablet (scored):** 30 mg; 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol [c]	***Injection:** 180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6.5.5.2 *American trypanosomiasis*

benznidazole	**Tablet:** 12.5 mg [c] **Tablet (scored):** 50 mg; 100 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.6 Medicines for ectoparasitic infections

ivermectin	**Tablet:** 3 mg

6.7 Medicines for Ebola virus disease

ansuvimab	**Powder for injection:** 400 mg
atoltivimab + maftivimab + odesivimab	**Injection:** 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial.

6.8 Medicines for COVID-19

WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.

Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.

The latest WHO Therapeutics and COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/nBkO1E

The latest WHO Drugs to prevent COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/L6RxYL

7. MEDICINES FOR CYSTIC FIBROSIS

elexacaftor + tezacaftor + ivacaftor	**Granules:** 80 mg + 40 mg + 60 mg; 100 mg + 50 mg + 75 mg in sachet. **Tablet:** 50 mg + 25 mg + 37.5 mg; 100 mg + 50 mg + 75 mg.
ivacaftor	**Granules:** 59.5 mg; 75 mg in sachet. **Tablet:** 75 mg; 150 mg.

Complementary List

pancreatic enzymes ***[c]***	***Capsule (modified release)*:*** *10 000 lipase units + 8000 amylase units + 600 protease units; 25 000 lipase units + 18 000 amylase units + 1000 protease units.* ** Units expressed in Ph.Eur*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Complementary List

☐ *adalimumab** *Therapeutic alternatives*:* – *certolizumab pegol* – *etanercept* – *golimumab* – *infliximab* * *including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL [c] ; 20 mg/0.2 mL [c] ; 20 mg/0.4 mL [c] ; 40 mg/0.4 mL; 40 mg/0.8 mL; 80 mg/0.8 mL in pre-filled syringe or pre-filled pen.*
azathioprine	***Oral liquid:*** *10 mg/mL [c] .* ***Powder for injection:*** *50 mg [c] ; 100 mg (as sodium salt) in vial.* ***Tablet:*** *25 mg [c] .* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/mL in 1 mL ampoule.* ***Oral liquid:*** *100 mg/mL [c] .*
tacrolimus	***Capsule (immediate-release):*** *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.* ***Granules for oral supsension:*** *0.2 mg; 1 mg.* ***Injection:*** *5 mg/mL in 1 mL vial.*

8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide	***Concentrate for solution for infusion:*** *1 mg/mL; 2 mg/mL.* – *Acute promyelocytic leukaemia*
*asparaginase** * *including quality-assured biosimilars*	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
bendamustine	***Injection:*** *45 mg/0.5 mL; 180 mg/2 mL.* – *Chronic lymphocytic leukaemia* – *Follicular lymphoma*
bleomycin	***Powder for injection:*** *15 000 IU (as sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
calcium folinate (leucovorin calcium)	***Injection:*** *3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule.* ***Tablet:*** *5 mg; 15 mg; 25 mg.* – *Burkitt lymphoma* – *Early stage colon cancer* – *Early stage rectal cancer* – *Gestational trophoblastic neoplasia* – *Metastatic colorectal cancer* – *Osteosarcoma*
capecitabine	***Tablet:*** *150 mg; 500 mg.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic breast cancer* – *Metastatic colorectal cancer*
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Cervical cancer* – *Early stage breast cancer* – *Epithelial ovarian cancer* – *Head and neck cancer (as a radio-sensitizer)* – *Low-grade glioma* – *Nasopharyngeal cancer* – *Nephroblastoma (Wilms tumour)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Testicular germ cell tumour*
chlorambucil	***Tablet:*** *2 mg.* – *Chronic lymphocytic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.* – *Cervical cancer* – *Head and neck cancer (as a radio-sensitizer)* – *Low-grade glioma* – *Nasopharyngeal cancer (as a radio-sensitizer)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* ***Solid oral dosage form:*** *25 mg, 50 mg.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Ewing sarcoma* – *Follicular lymphoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Low-grade glioma* – *Metastatic breast cancer* – *Multiple myeloma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
cytarabine	***Injection:*** *100 mg in vial.* ***Powder for injection:*** *100 mg in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Langerhans cell histiocytosis*
dacarbazine	***Powder for injection:*** *100 mg; 200 mg in vial.* – *Hodgkin lymphoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Ewing sarcoma* – *Gestational trophoblastic neoplasia* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
daunorubicin	***Injection:*** *2 mg/mL; 5 mg/mL (as hydrochloride) in vial.* ***Powder for injection:*** *20 mg; 50 mg (as hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia*
docetaxel	***Injection:*** *20 mg/mL; 40 mg/mL.* – *Early stage breast cancer* – *Metastatic breast cancer* – *Metastatic prostate cancer*
doxorubicin	***Injection:*** *2 mg/mL (hydrochloride) in vial.* ***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Early stage breast cancer* – *Ewing sarcoma* – *Follicular lymphoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Metastatic breast cancer* – *Multiple myeloma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma*
doxorubicin (as pegylated liposomal)	***Injection:*** *2 mg/mL (hydrochloride) in 10 mL, 25 mL vial.* – *Kaposi sarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
etoposide	***Capsule:*** *50 mg, 100 mg.* ***Injection:*** *20 mg/mL in 5 mL ampoule.* ***Powder for injection:*** *100 mg (as phosphate) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Ewing sarcoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Nephroblastoma (Wilms tumour)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Testicular germ cell tumour*
fludarabine	***Powder for injection:*** *50 mg (phosphate) in vial.* ***Tablet:*** *10 mg* – *Chronic lymphocytic leukaemia.*
fluorouracil	***Injection:*** *50 mg/mL in vial.* – *Early stage breast cancer* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*
gemcitabine	***Powder for injection:*** *200 mg; 1 g in vial.* – *Epithelial ovarian cancer* – *Non-small cell lung cancer*
hydroxyurea (hydroxycarbamide)	***Solid oral dosage form:*** *100 mg [c] ; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.* – *Chronic myeloid leukaemia*
ifosfamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Rhabdomyosarcoma* – *Testicular germ cell tumour*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
irinotecan	***Injection:*** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.* – *Metastatic colorectal cancer* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
melphalan	***Tablet:*** *2 mg.* ***Powder for injection:*** *50 mg in vial.* – *Multiple myeloma*
mercaptopurine	***Tablet:*** *50 mg.* ***Oral liquid:*** *20 mg/mL* **[c]** . – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Langerhans cell histiocytosis*
methotrexate	***Concentrated injection:*** *1000 mg/10 mL.* ***Injection:*** *50 mg/2 mL.* ***Powder for injection:*** *50 mg (as sodium) in vial.* ***Tablet:*** *2.5 mg (as sodium).* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Early stage breast cancer* – *Gestational trophoblastic neoplasia* – *Langerhans cell histiocytosis* – *Osteosarcoma*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.* ***Powder for injection:*** *50 mg; 100 mg in vial.* – *Early stage colon cancer* – *Metastatic colorectal cancer*
paclitaxel	***Injection:*** *6 mg/mL in vial.* – *Cervical cancer* – *Epithelial ovarian cancer* – *Early stage breast cancer* – *Metastatic breast cancer* – *Kaposi sarcoma* – *Nasopharyngeal cancer* – *Non-small cell lung cancer* – *Ovarian germ cell tumour*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
*pegaspargase** * *including quality-assured biosimilars*	***Injection:*** *3750 units/5 mL in vial.* ***Powder for injection:*** *3750 units in vial.* – *Acute lymphoblastic leukaemia*
procarbazine [c]	***Capsule:*** *50 mg (as hydrochloride).* – *Hodgkin lymphoma*
realgar-Indigo naturalis formulation	***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).* – *Acute promyelocytic leukaemia*
tioguanine [c]	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*
vinblastine	***Injection:*** *10 mg/10 mL (sulfate) in vial.* ***Powder for injection:*** *10 mg (sulfate) in vial.* – *Anaplastic large cell lymphoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Langerhans cell histiocytosis* – *Low-grade glioma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
vincristine	***Injection:*** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.* ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Follicular lymphoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Langerhans cell histiocytosis* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Retinoblastoma* – *Rhabdomyosarcoma*
vinorelbine	***Capsule:*** *20 mg; 30 mg; 80 mg.* ***Injection:*** *10 mg/mL in 1 mL, 5 mL vial.* – *Metastatic breast cancer* – *Non-small cell lung cancer* – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.2 *Targeted therapies*

Complementary List

all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* – *Acute promyelocytic leukaemia*
bortezomib	***Powder for injection:*** *3.5 mg in vial.* – *Multiple myeloma*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
☐ *erlotinib* *Therapeutic alternatives:* – *afatinib* – *gefitinib*	***Tablet:*** *100 mg, 150 mg.* – *EGFR mutation-positive advanced non-small cell lung cancer*
everolimus	***Tablet:*** *2.5 mg; 5 mg; 7.5 mg; 10 mg.* ***Tablet (dispersible):*** *2 mg; 3 mg; 5 mg.* – *Subependymal giant cell astrocytoma*
☐ *ibrutinib* *Therapeutic alternatives:* – *zanubrutinib*	***Capsule:*** *140 mg.* – *Relapsed/refractory chronic lymphocytic leukaemia/ small lymphocytic lymphoma*
imatinib	***Solid oral dosage form:*** *100 mg; 400 mg.* – *Chronic myeloid leukaemia* – *Gastrointestinal stromal tumour* – *Philadelphia chromosome positive acute lymphoblastic leukaemia*
nilotinib	***Capsule:*** *150 mg; 200 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
*rituximab** * *including quality-assured biosimilars*	***Injection (intravenous):*** *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Chronic lymphocytic leukaemia* – *Follicular lymphoma*
*trastuzumab** * *including quality-assured biosimilars*	***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial.* – *Early stage HER2 positive breast cancer* – *Metastatic HER2 positive breast cancer*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.3 *Immunomodulators*

Complementary List

*blinatumomab** * *including quality-assured biosimilars*	***Powder for concentrate for solution for infusion:*** *35 micrograms; 38.5 micrograms in vial.* – *B-cell acute lymphoblastic leukemia*
*filgrastim** * *including quality-assured biosimilars*	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.* ***Injection:*** *300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
lenalidomide	***Capsule:*** *25 mg.* – *Multiple myeloma*
*pegfilgrastim** * *including quality-assured biosimilars*	***Injection:*** *6 mg/0.6 mL in pre-filled syringe.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
*pembrolizumab** * *including quality-assured biosimilars*	***Concentrate for solution for infusion:*** *25 mg/mL in 4 mL vial.* – *Metastatic cervical cancer ≥ 1% PD-L1expression*^ ^ *in combination with platinum-based themotherapy* – *Metastatic colorectal cancer*# # *as monotherapy for deficient mismatch repair (dMMR) / microsatellite instability-high (MSI-H) tumours*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

☐ *pembrolizumab**	***Concentrate for solution for infusion:*** *25 mg/mL in 4 mL vial.*
Therapeutic alternatives: – *atezolizumab** – *cemiplimab**	– *Metastatic non-small cell lung cancer, oncogene-driver wild-type and≥ 50% PD-L1 expression^* ^ *as monotherapy*
* *including quality-assured biosimilars*	
☐ *pembrolizumab**	***Concentrate for solution for infusion:*** *25 mg/mL in 4 mL vial.*
Therapeutic alternatives: – *nivolumab**	– *Metastatic melanoma^* ^ *as monotherapy*
* *including quality-assured biosimilars*	
thalidomide	***Capsule:*** *50 mg.* – *Multiple myeloma*

8.2.4 ***Hormones and antihormones***

Complementary List

☐ *abiraterone*	***Tablet:*** *250 mg; 500 mg.*
Therapeutic alternatives: – *enzalutamide*	– *Metastatic castration-resistant prostate cancer*
☐ *anastrozole*	***Tablet:*** *1 mg.*
Therapeutic alternatives: – *4th level ATC chemical subgroup (L02BG Aromatase inhibitors)*	– *Early stage breast cancer* – *Metastatic breast cancer*
☐ *bicalutamide*	***Tablet:*** *50 mg.*
Therapeutic alternatives: – *flutamide* – *nilutamide*	– *Metastatic prostate cancer*
dexamethasone	***Injection:*** *4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule.* ***Oral liquid:*** *2 mg/5 mL (as sodium phosphate)* **[c]** . ***Tablet:*** *2 mg* **[c]** *; 4 mg (as dexamethasone base).* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Multiple myeloma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
☐ *leuprorelin* *Therapeutic alternatives:* – *goserelin* – *triptorelin*	***Injection:*** *7.5 mg; 22.5 mg in pre-filled syringe.* – *Early stage breast cancer* – *Metastatic prostate cancer*
methylprednisolone [c]	***Powder for injection:*** *40 mg (as sodium succinate); 125 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukamia* – *Burkitt lymphoma*
☐ *prednisolone* *Therapeutic alternatives:* – *prednisone*	***Oral liquid:*** *5 mg/mL* [c] ***Tablet:*** *5 mg; 25 mg.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Chronic lymphocytic leukaemia* – *Diffuse large B-cell lymphoma* – *Follicular lymphoma* – *Hodgkin lymphoma* – *Langerhans cell histiocytosis* – *Metastatic castration-resitsant prostate cancer* – *Multiple myeloma*
tamoxifen	***Tablet:*** *10 mg; 20 mg (as citrate).* – *Early stage breast cancer* – *Metastatic breast cancer*

8.2.5 ***Supportive medicines***

Complementary List

allopurinol [c]	***Powder for injection:*** *500 mg (as sodium).* ***Tablet:*** *100 mg; 300 mg.* – *Tumour lysis syndrome*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
mesna	***Injection*:*** *100 mg/mL in 2 mL, 4 mL, 10 mL ampoule.* ***Tablet:*** *400 mg; 600 mg.* * May also be used for oral administration. – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Rhabdomyosarcoma* – *Testicular germ cell tumour*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg (with 1 mL solvent); 7.5 mg (with 5 mL solvent) in vial.* – *Tumour lysis syndrome*
zoledronic acid	***Concentrate solution for infusion:*** *4 mg/5 mL in 5 mL vial.* ***Solution for infusion:*** *4 mg/100 mL in 100 mL bottle.* – *Malignancy-related bone disease*
9. THERAPEUTIC FOODS	
ready-to-use therapeutic food [c]	**Biscuit or paste*** * of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	**Oral liquid:** equivalent to 9 mg/mL elemental iron [c]; equivalent to 25 mg/mL elemental iron. **Tablet:** equivalent to 60 mg – 65 mg elemental iron.
ferrous salt + folic acid	**Tablet:** equivalent to 60 mg elemental iron + 400 micrograms folic acid.* * nutritional supplement for use during pregnancy **Tablet:** equivalent to 60 mg elemental iron + 2.8 mg folic acid.** **for weekly iron and folic acid supplementation

10. MEDICINES AFFECTING THE BLOOD *(continued)*

folic acid	**Oral liquid:** 1 mg/mL [c]. **Tablet:** 400 micrograms*; 1 mg; 5 mg. * periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	**Injection:** 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

Complementary List

☐ *erythropoiesis-stimulating agents** *Therapeutic alternatives:* – *epoetin alfa, beta and theta* – *darbepoetin alfa* – *methoxy polyethylene glycol-epoetin beta* * *including quality-assured biosimilars*	***Injection: pre-filled syringe*** *1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8 mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.*

10.2 Medicines affecting coagulation

☐ dabigatran Therapeutic alternatives: – apixaban – edoxaban – rivaroxaban	**Capsule:** 110 mg; 150 mg.
desmopressin [c]	**Injection:** 4 micrograms/mL (acetate) in 1 mL ampoule. **Nasal spray:** 150 micrograms (acetate) per actuation.
emicizumab	**Injection:** 12 mg/0.4 mL [c]; 30 mg/mL [c]; 60 mg/0.4 mL; 105 mg/0.7 mL; 150 mg/mL; 300 mg/2 mL in vial.
☐ enoxaparin* Therapeutic alternatives*: – dalteparin – nadroparin * including quality-assured biosimilars	**Injection: ampoule or pre-filled syringe** 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
heparin sodium	**Injection:** 1000 IU/mL; 5000 IU/mL; 20 000 IU/mL in 1 mL ampoule or vial.

10. MEDICINES AFFECTING THE BLOOD *(continued)*

phytomenadione	**Injection:** 1 mg/0.5mL [c]; 1 mg/mL [c]; 10 mg/mL in ampoule. **Injection (mixed micelle solution):** 2 mg/0.2 mL; 10 mg/mL in ampoule. **Tablet:** 5 mg.
protamine sulfate	**Injection:** 10 mg/mL in 5 mL ampoule or vial.
tranexamic acid	**Injection:** 100 mg/mL in 10 mL ampoule.
☐ warfarin Therapeutic alternatives: – acenocoumarol	**Tablet (scored):** 1 mg; 2 mg; 3 mg; 5 mg (sodium).
Complementary List	
heparin sodium [c]	***Injection:*** *1000 IU/mL; 5000 IU/mL in 1 mL ampoule or vial.*
protamine sulfate [c]	***Injection:*** *10 mg/mL in 5 mL ampoule or vial.*
☐ *warfarin [c]* *Therapeutic alternatives:* – *acenocoumarol*	***Tablet:*** *0.5 mg; 1 mg; 2 mg; 3 mg; 5 mg (sodium).*

10.3 Medicines for haemoglobinopathies

10.3.1 ***Medicines for sickle-cell disease***

☐ deferasirox Therapeutic alternatives: – deferiprone	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg. **Tablet (film-coated):** 90 mg; 180 mg; 360 mg.
hydroxyurea (hydroxycarbamide)	**Solid oral dosage form:** 100 mg [c]; 200 mg; 500 mg; 1 g.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*

10.3.2 ***Medicines for thalassaemias***

☐ deferasirox Therapeutic alternatives: – deferiprone	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg. **Tablet (film-coated):** 90 mg; 180 mg; 360 mg.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*

11. BLOOD PRODUCTS, COAGULATION FACTORS, AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population.

All blood and plasma-derived products should comply with the WHO requirements.

☐ cryoprecipitate, pathogen-reduced Therapeutic alternatives: – cryoprecipitate, native* * native cryoprecipitate should only be used in situations of life-threatening haemorrhage when pathogen-reduced cryoprecipitate is not available.	**Injection:** frozen liquid in bag or lyophilized powder in vial containing: – > 50 IU Factor VIII – > 100 IU vWF – > 140 mg clottable fibrinogen per unit
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	

11.2 Human immunoglobulins

anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	
normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.* ***Subcutaneous administration:*** *15%; 16% protein solution.* – *Primary immune deficiency* ***Intravenous administration:*** *5%; 10% protein solution.* – *Primary immune deficiency* – *Kawasaki disease* – *Langerhans cell histiocytosis*

11. BLOOD PRODUCTS, COAGULATION FACTORS, AND PLASMA SUBSTITUTES *(continued)*

11.3 *Coagulation factors*

coagulation factor VIII, plasma-derived	**Powder for injection:** 250 IU; 500 IU; 1000 IU in vial.
coagulation factor IX, plasma-derived	**Powder for injection:** 500 IU; 1000 IU in vial.
coagulation factor VIII, recombinant	**Lyophilized powder for solution for injection:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU in vial.
coagulation factor IX, recombinant	**Lyophilized powder for solution for injection:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU in vial.

11.4 Plasma substitutes

☐ dextran 70	**Injectable solution:** 6%.
Therapeutic alternatives: – Polygeline injectable solution 3.5%	

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – carvedilol – metoprolol	
glyceryl trinitrate	**Tablet (sublingual):** 500 micrograms.
isosorbide dinitrate	**Tablet (sublingual):** 5 mg.
verapamil	**Tablet:** 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – carvedilol – metoprolol	
digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.

12. CARDIOVASCULAR MEDICINES *(continued)*	
epinephrine (adrenaline)	**Injection:** 100 micrograms/mL (as acid tartrate or hydrochloride) in 10 mL ampoule.
lidocaine	**Injection:** 20 mg/mL (hydrochloride) in 5 mL ampoule.
verapamil	**Injection:** 2.5 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 40 mg; 80 mg (hydrochloride).
Complementary List	
amiodarone	***Injection:*** *50 mg/mL (hydrochloride) in 3 mL ampoule.* ***Tablet:*** *100 mg; 200 mg; 400 mg (hydrochloride).*

12.3 Antihypertensive medicines

☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	**Tablet:** 5 mg (as maleate, mesylate or besylate).
☐ bisoprolol Therapeutic alternatives: – atenolol* – carvedilol – metoprolol	**Tablet:** 1.25 mg; 5 mg. * atenolol should not be used as a first-line agent in uncomplicated hypertension in patients > 60 years
☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Oral liquid:** 1 mg/mL (as hydrogen maleate) [c]. **Tablet:** 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
hydralazine*	**Powder for injection:** 20 mg (hydrochloride) in ampoule. **Tablet:** 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlorthalidone – indapamide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 12.5 mg; 25 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ lisinopril + ☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg.
☐ lisinopril + ☐ hydrochlorothiazide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Tablet:** 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg.
☐ losartan Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	**Tablet:** 25 mg; 50 mg; 100 mg.
methyldopa*	**Tablet:** 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ perindopril + ☐ amlodipine + ☐ indapamide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for perindopril) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine) – chlorthalidone, chlorothiazide, hydrochlorothiazide (for indapamide)	**Solid oral dosage form:** 5 mg (arginine) + 5 mg + 1.25 mg; 5 mg (arginine) + 10 mg + 1.25 mg; 10 mg (arginine) + 5 mg + 2.5 mg; 10 mg (arginine) + 10 mg + 2.5 mg.
☐ telmisartan + ☐ amlodipine Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg.
☐ telmisartan + ☐ hydrochlorothiazide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Tablet:** 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ valsartan + ☐ amlodipine + ☐ hydrochlorothiazide Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for valsartan) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Solid oral dosage form:** 160 mg + 5 mg + 12.5 mg; 160 mg + 5 mg + 25 mg; 160 mg + 10 mg + 12.5 mg; 160 mg + 10 mg + 25 mg; 320 mg + 10 mg + 25 mg.

Complementary List

sodium nitroprusside	***Powder for infusion:*** *50 mg in ampoule.*

12.4 Medicines used in heart failure

☐ bisoprolol Therapeutic alternatives: – carvedilol – metoprolol	**Tablet:** 1.25 mg; 5 mg.
digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Tablet:** 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
☐ furosemide Therapeutic alternatives: – bumetanide – torasemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule. **Oral liquid:** 20 mg/5 mL; 50 mg/5 mL [c]. **Tablet:** 20 mg; 40 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*	
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlorthalidone – indapamide	**Oral liquid:** 50 mg/5 mL. **Solid oral dosage form:** 25 mg.
☐ losartan Therapeutic alternatives: – 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)	**Tablet:** 25 mg; 50 mg; 100 mg.
spironolactone	**Tablet:** 25 mg.
Complementary List	
digoxin ***[c]***	***Injection:*** *100 micrograms/mL in 1 mL ampoule; 250 micrograms/mL in 2 mL ampoule.* ***Oral liquid:*** *50 micrograms/mL.* ***Tablet:*** *62.5 micrograms; 125 micrograms; 250 micrograms.*
dopamine	***Injection:*** *40 mg/mL (hydrochloride) in 5 mL vial.*
12.5 Antithrombotic medicines	
12.5.1 ***Anti-platelet medicines***	
acetylsalicylic acid	**Tablet:** 100 mg.
clopidogrel	**Tablet:** 75 mg; 300 mg.
12.5.2 ***Thrombolytic medicines***	
Complementary List	
alteplase	***Powder for injection:*** *10 mg; 20 mg; 50 mg in vial*
streptokinase	***Powder for injection:*** *1.5 million IU in vial.*

12. CARDIOVASCULAR MEDICINES *(continued)*

12.6 Lipid-lowering agents

☐ simvastatin*	**Tablet:** 5 mg; 10 mg; 20 mg; 40 mg.
Therapeutic alternatives: – atorvastatin – fluvastatin – lovastatin – pravastatin	* For use in high-risk patients.

12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

acetylsalicylic acid + ☐ atorvastatin + ☐ ramipril Therapeutic alternatives: – fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin) – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for ramipril)	**Tablet:** 100 mg + 20 mg + 2.5 mg; 100 mg + 20 mg + 5 mg; 100 mg + 20 mg + 10 mg; 100 mg + 40 mg + 2.5 mg; 100 mg + 40 mg + 5 mg; 100 mg + 40 mg + 10 mg.
acetylsalicylic acid + ☐ simvastatin + ☐ ramipril + ☐ atenolol + ☐ hydrochlorothiazide Therapeutic alternatives: – atorvastatin, fluvastatin, lovastatin, pravastatin (for simvastatin) – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for ramipril) – bisoprolol, carvedilol, metoprolol (for atenolol) – chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)	**Tablet:** 100 mg + 20 mg + 5 mg + 50 mg + 12.5 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*	
☐ atorvastatin + ☐ perindopril + ☐ amlodipine Therapeutic alternatives: – fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin) – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for perindopril) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 20 mg + 5 mg + 5 mg; 20 mg + 10 mg + 10 mg; 40 mg + 5 mg + 5 mg; 40 mg + 10 mg + 10 mg.
13. DERMATOLOGICAL MEDICINES	
13.1 Antifungal medicines	
☐ miconazole Therapeutic alternatives: – 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
sodium thiosulfate	**Solution:** 15%.
terbinafine	**Cream or ointment:** 1% (hydrochloride).
13.2 Anti-infective medicines	
mupirocin	**Cream:** 2% (as calcium). **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] > 2 months.

13. DERMATOLOGICAL MEDICINES *(continued)*

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine	**Lotion.**
☐ hydrocortisone Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))	**Cream or ointment:** 1% (acetate).

13.4 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	**Cream or lotion:** 5%.
☐ calcipotriol Therapeutic alternatives: – calcitriol – tacalcitol	**Cream or ointment:** 50 micrograms/mL (0.005%). **Lotion:** 50 micrograms/mL (0.005%).
coal tar	**Solution:** 5%.
fluorouracil	**Ointment:** 5%.
☐ podophyllum resin Therapeutic alternatives: – podophyllotoxin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.

Complementary List

☐ *adalimumab** *Therapeutic alternatives:* – *certolizumab pegol* – *etanercept* – *infliximab* * *including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL [c]; 20 mg/0.2 mL [c]; 20 mg/0 .4 mL [c]; 40 mg/0.4 mL; 40 mg/0.8 mL; 80 mg/0.8 mL in pre-filled syringe or pre-filled pen.*

13. DERMATOLOGICAL MEDICINES *(continued)*	
methotrexate	***Tablet:** 2.5 mg; 10 mg (as sodium).*
*ustekinumab** * *including quality-assured biosimilars*	***Injection:** 45 mg/0.5 mL in vial, pre-filled syringe, or pre-filled pen; 90 mg/mL in pre-filled syringe or pre-filled pen.*
13.5 Scabicides and pediculicides	
☐ benzyl benzoate [a] Therapeutic alternatives: – precipitated sulfur topical ointment	**Lotion:** 25%. [a] > 2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.
13.6 Moisturizers	
urea	**Cream:** 5%
glycerol	**Cream:** 15% to 20%.
13.7 Sunscreens	
sunscreen, broad-spectrum	**Topical:** Therapeutic broad-spectrum sunscreens should contain proven active ingredients in appropriate amounts to absorb or filter UVA and UVB radiation, and have a high sun protection factor (SPF).
14. DIAGNOSTIC AGENTS	
14.1 Ophthalmic medicines	
fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide Therapeutic alternatives: – atropine – cyclopentolate	**Eye drops:** 0.5%.
14.2 Radiocontrast media	
☐ amidotrizoate Therapeutic alternatives to be reviewed	**Injection:** 140 mg to 420 mg iodine/mL (as sodium or meglumine salt) in 20 mL ampoule.
barium sulfate	**Aqueous suspension.**

14. DIAGNOSTIC AGENTS *(continued)*	
☐ iohexol Therapeutic alternatives to be reviewed	**Injection:** 140 mg to 350 mg iodine/mL in 5 mL; 10 mL; 20 mL ampoule.
Complementary List	
barium sulfate ***[c]***	***Aqueous suspension.***
☐ *meglumine iotroxate* *Therapeutic alternatives to be reviewed*	***Solution:*** *5 g to 8 g iodine in 100 mL to 250 mL.*

15. ANTISEPTICS AND DISINFECTANTS	
15.1 Antiseptics	
☐ chlorhexidine Therapeutic alternatives to be reviewed	**Solution:** 5% (digluconate).
☐ ethanol Therapeutic alternatives: – propanol	**Solution:** 70% (denatured).
☐ povidone iodine Therapeutic alternatives: – iodine	**Solution:** 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	**Solution:** containing ethanol 80% volume/volume. **Solution:** containing isopropyl alcohol 75% volume/volume.
chlorine base compound	**Liquid:** (0.1% available chlorine) for solution. **Powder:** (0.1% available chlorine) for solution. **Solid:** (0.1% available chlorine) for solution.
☐ chloroxylenol Therapeutic alternatives: – 4th level ATC chemical subgroup (D08AE Phenol and derivatives)	**Solution:** 4.8%.
glutaral	**Solution:** 2%.

15. ANTISEPTICS AND DISINFECTANTS *(continued)*	
hypochlorous acid	**Solution (aqueous):** containing hypochlorous acid ≥ 150 parts per million.
16. DIURETICS	
amiloride	**Tablet:** 5 mg (hydrochloride).
☐ furosemide Therapeutic alternatives: – bumetanide – torasemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule. **Oral liquid:** 20 mg/5 mL; 50 mg/5 mL [c]. **Tablet:** 20 mg; 40 mg.
☐ hydrochlorothiazide Therapeutic alternatives: – chlorothiazide – chlortalidone – indapamide	**Solid oral dosage form:** 25 mg.
mannitol	**Injectable solution:** 10%; 20%.
spironolactone	**Tablet:** 25 mg.
Complementary List	
☐ *hydrochlorothiazide [c]* *Therapeutic alternatives:* – *chlorothiazide* – *chlortalidone*	***Solid oral dosage form:** 12.5 mg [c]; 25 mg.*
mannitol [c]	***Solution for infusion:** 10%; 20%.*
spironolactone [c]	***Oral liquid:** 25 mg/5 mL.* ***Tablet:** 12.5 mg; 25 mg.*
17. GASTROINTESTINAL MEDICINES	
Complementary List	
pancreatic enzymes [c]	*C**apsule (modified release)*:** 10 000 lipase units + 8000 amylase units + 600 protease units; 25 000 lipase units + 18 000 amylase units + 1000 protease units.* * *Units expressed in Ph.Eur*

17. GASTROINTESTINAL MEDICINES *(continued)*

17.1 Antiulcer medicines

☐ omeprazole Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	**Powder for injection:** 40 mg in vial. **Powder for oral liquid:** 1 mg/mL; 4 mg/mL. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BA H_2-receptor antagonists) excluding combinations	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg; 0.75 mg; 1.5 mg; 2 mg; 4 mg (as dexamethasone base).
metoclopramide	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL [c]. **Tablet (scored):** 10 mg (hydrochloride).
☐ ondansetron Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg/mL in 2 mL, 4 mL ampoule (as hydrochloride dihydrate). **Oral liquid:** 4 mg/5 mL (as hydrochloride dihydrate). **Solid oral dosage form:** 4 mg; 8 mg; 24 mg (as hydrochloride dihydrate).
Complementary list	
aprepitant	***Capsule:*** *80 mg; 125 mg; 165 mg.* ***Powder for oral suspension:*** *125 mg in sachet.*

17. GASTROINTESTINAL MEDICINES *(continued)*

17.3 Anti-inflammatory medicines

☐ sulfasalazine	**Retention enema:** 3 g/100 mL.
Therapeutic alternatives:	**Suppository:** 500 mg.
– mesalazine	**Tablet:** 500 mg.
Complementary List	
hydrocortisone	***Retention enema:*** *100 mg/60 mL.*
	Suppository: *25 mg (acetate).*
prednisolone	***Retention enema:*** *20 mg/100 mL (as sodium phosphate).*

17.4 Laxatives

☐ senna	**Tablet:** 7.5 mg (sennosides) (or traditional dosage forms).
Therapeutic alternatives:	
– bisacodyl	

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate [C]	**Co-package containing:** **ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **tablet (dispersible, scored):** 20 mg (see Section 17.5.2)

17.5.1 *Oral rehydration*

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mEq or mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17. GASTROINTESTINAL MEDICINES *(continued)*

17.5.2 *Medicines for diarrhoea*

zinc sulfate*	**Tablet (dispersible, scored):** 20 mg.

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	**Oral liquid:** 100 micrograms (acetate) [c] . **Tablet:** 100 micrograms (acetate).
hydrocortisone	**Granules:** 0.5 mg; 1 mg; 2 mg; 5 mg in capsule [c] . **Tablet:** 5 mg; 10 mg; 20 mg.
☐ prednisolone Therapeutic alternatives: – prednisone	**Tablet:** 1 mg.

18.2 Androgens

Complementary List

testosterone	***Injection:** 200 mg (enanthate) in 1 mL ampoule.*

18.3 Estrogens

18.4 Progestogens

☐ medroxyprogesterone acetate Therapeutic alternatives: – norethisterone	**Tablet:** 5 mg.

18.5 Medicines for diabetes

18.5.1 *Insulins*

☐ insulin (analogue, long-acting)* Therapeutic alternatives: – insulin glargine – insulin degludec – insulin detemir	**Injection solution:** 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.

* including quality-assured biosimilars

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

☐ insulin (analogue, rapid-acting)* Therapeutic alternatives: – insulin lispro – insulin aspart – insulin glulisine * including quality-assured biosimilars	**Injection solution:** 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
insulin (human, intermediate-acting)* * *including quality-assured biosimilars*	**Injection suspension:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).
insulin (human, short-acting)* * *including quality-assured biosimilars*	**Injection solution:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.

18.5.2 ***Hypoglycaemic agents***

☐ empagliflozin Therapeutic alternatives: – canagliflozin – dapagliflozin	**Tablet:** 10 mg; 25 mg.
☐ gliclazide* Therapeutic alternatives: – 4th level ATC chemical subgroup (A10BB Sulfonylureas)	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
metformin	**Tablet:** 500 mg (hydrochloride).
☐ semaglutide* Therapeutic alternatives: – dulaglutide – liraglutide – tirzepatide * including quality-assured biosimilars	**Injection solution:** 0.68 mg/mL; 1.34 mg/mL; 2.68 mg/mL.
Complementary List	
metformin ***[c]***	***Tablet:*** *500 mg (hydrochloride).*

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

18.6 Medicines for hypoglycaemia

glucagon	**Injection:** 1 mg/mL as powder and diluent.

Complementary List

diazoxide [c]	***Oral liquid:*** *50 mg/mL.* ***Tablet:*** *50 mg.*

18.7 Thyroid hormones and antithyroid medicines

levothyroxine	**Tablet:** 25 micrograms [c]; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet (scored):** 60 mg.
☐ methimazole Therapeutic alternatives: – carbimazole (depending on local availability)	**Tablet:** 5mg, 10mg.
propylthiouracil*	**Tablet:** 50 mg. * For use when alternative first-line treatment is not appropriate or available; and in patients during the first trimester of pregnancy.

Complementary List

iodine + potassium iodide (Lugol's solution) [c]	***Oral liquid (aqueous):*** *5% w/v + 10% w/v.*
☐ *methimazole* [c] *Therapeutic alternatives:* – *carbimazole (depending on local availability)*	***Tablet:*** *5mg, 10mg.*
potassium iodide [c]	***Tablet (scored):*** *65 mg.*
*propylthiouracil** [c]	***Tablet:*** *50 mg.* * *For use when alternative first-line treatment is not appropriate or available.*

18.8 Medicines for disorders of the pituitary hormone system

☐ cabergoline Therapeutic alternatives: – bromocriptine	**Tablet:** 0.5 mg; 1 mg.

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

Complementary List

octreotide	***Injection (immediate-release):*** *0.05 mg/mL; 0.1 mg/mL; 0.5 mg/mL (as acetate) in 1 mL vial.* ***Injection (modified-release):*** *20 mg (as acetate) in vial plus diluent.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection.**

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus monoclonal antibodies* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). **Injection:** 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	**Injection.** * Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	**Injection:** 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial.

19. IMMUNOLOGICALS *(continued)*

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts (SAGE) on Immunization.

WHO vaccine position papers are periodically revised to assess the need for an update. The list below details the vaccines for which there is a recommendation from WHO and a corresponding WHO vaccine position paper as at May 2025. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Vaccines included on the Model Lists reflect the recommendations of SAGE, as per the available policy reflected in the WHO vaccine position papers.

Countries are encouraged to consider inclusion of specific vaccines into their national immunization schedule based on national priorities by carefully assessing various criteria such as local burden of disease and disease epidemiology, acceptability, cost, cost-effectiveness, programmatic feasibility, regulatory status, and availability of products.

All vaccines should comply with the WHO requirements for biological substances.

BCG vaccine
cholera vaccine
dengue vaccine
diphtheria vaccine
Ebola vaccine
Haemophilus influenzae type b vaccine
hepatitis A vaccine
hepatitis B vaccine
hepatitis E vaccine
human papilloma virus (HPV) vaccine
influenza vaccine (seasonal)
Japanese encephalitis vaccine
malaria vaccine [c]
measles vaccine

19. IMMUNOLOGICALS *(continued)*

meningococcal meningitis vaccine
mpox vaccine
mumps vaccine
pertussis vaccine
pneumococcal vaccine
poliomyelitis vaccine
rabies vaccine
respiratory syncytial virus vaccine
rotavirus vaccine
rubella vaccine
tetanus vaccine
tick-borne encephalitis vaccine
typhoid vaccine
varicella vaccine
yellow fever vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

☐ atracurium Therapeutic alternatives to be reviewed	**Injection:** 10 mg/mL (besylate).
neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule.
☐ vecuronium [c] Therapeutic alternatives: – atracurium	**Powder for injection:** 10 mg (bromide) in vial.

Complementary List

pyridostigmine	***Injection:*** *5 mg/mL (bromide) in ampoule or vial.* ***Tablet (scored):*** *60 mg (bromide).*
☐ *vecuronium* *Therapeutic alternatives to be reviewed*	***Powder for injection:*** *10 mg (bromide) in vial.*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – *Trachoma*
erythromycin	**Ointment:** 0.5% [c]. – *Infections due to Chlamydia trachomatis or Neisseria gonorrhoea*
☐ gentamicin Therapeutic alternatives: – amikacin – kanamycin – netilmicin – tobramycin	**Solution (eye drops):** 0.3% (sulfate). – *Bacterial blepharitis* – *Bacterial conjunctivitis*
natamycin	**Suspension (eye drops):** 5%. – *Fungal keratitis*
☐ ofloxacin Therapeutic alternatives: – 4th level ATC chemical subgroup (S01AE Fluoroquinolones)	**Solution (eye drops):** 0.3%. – *Bacterial conjunctivitis* – *Bacterial keratitis*
☐ tetracycline Therapeutic alternatives: – chlortetracycline – oxytetracycline	**Eye ointment:** 1% (hydrochloride). – *Bacterial blepharitis* – *Bacterial conjunctivitis* – *Bacterial keratitis* – *Trachoma*

21.2 Anti-inflammatory agents

☐ prednisolone Therapeutic alternatives to be reviewed	**Solution (eye drops):** 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	**Solution (eye drops):** 0.5% (hydrochloride). [a] Not in preterm neonates.

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

21.4 Miotics and antiglaucoma medicines

acetazolamide	**Tablet:** 250 mg.
latanoprost	**Solution (eye drops):** 50 micrograms/mL.
☐ pilocarpine Therapeutic alternatives: – carbachol	**Solution (eye drops):** 2%; 4% (hydrochloride or nitrate).
☐ timolol Therapeutic alternatives: – 4th level ATC chemical subgroup (S01ED Beta blocking agents) excluding combinations	**Solution (eye drops):** 0.25%; 0.5% (as hydrogen maleate).

21.5 Mydriatics

☐ atropine [a] Therapeutic alternatives*: – cyclopentolate hydrochloride – homatropine hydrobromide * *EMLc only*	**Solution (eye drops):** 0.1%; 0.5%; 1% (sulfate). [a] > 3 months.

Complementary List

epinephrine (adrenaline)	***Solution (eye drops):** 2% (as hydrochloride).*

21.6 Anti-vascular endothelial growth factor (VEGF) preparations

Complementary List

*bevacizumab** * *including quality-assured biosimilars*	***Injection:** 25 mg/mL.*

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.1 Contraceptives

22.1.1 *Oral hormonal contraceptives*

☐ ethinylestradiol + ☐ levonorgestrel Therapeutic alternatives to be reviewed	**Tablet:** 30 micrograms + 150 micrograms.

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*	
☐ ethinylestradiol + ☐ norethisterone	**Tablet:** 35 micrograms + 1 mg.
Therapeutic alternatives to be reviewed	
levonorgestrel	**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	**Tablet:** 30 mg (as acetate).
22.1.2 ***Injectable hormonal contraceptives***	
estradiol cypionate + medroxyprogesterone acetate	**Injection:** 5 mg + 25 mg.
medroxyprogesterone acetate	**Injection (intramuscular):** 150 mg mL in 1 mL vial. **Injection (subcutaneous):** 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	**Oily solution:** 200 mg/mL in 1 mL ampoule.
22.1.3 ***Intrauterine devices***	
copper-containing device	
levonorgestrel-releasing intrauterine system	**Intrauterine system:** with reservoir containing 52 mg of levonorestrel
22.1.4 ***Barrier methods***	
condoms	
diaphragms	
22.1.5 ***Implantable contraceptives***	
etonogestrel-releasing implant	**Single-rod etonogestrel-releasing implant:** containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	**Two-rod levonorgestrel-releasing implant:** each rod containing 75 mg of levonorgestrel (150 mg total).

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.1.6 *Intravaginal contraceptives*

ethinylestradiol + etonogestrel	**Vaginal ring:** containing 2.7 mg + 11.7 mg.
progesterone vaginal ring*	**Progesterone-releasing vaginal ring:** containing 2.074 g of micronized progesterone. * For use in women actively breastfeeding at least 4 times per day.

22.2 Ovulation inducers

Complementary List

clomifene	***Tablet:*** *50 mg (citrate).*
☐ *letrozole* *Therapeutic alternatives:* – *anastrozole*	***Solid oral dosage form:*** *2.5 mg.*

22.3 Uterotonics

carbetocin	**Injection (heat stable):** 100 micrograms/mL.
☐ ergometrine Therapeutic alternatives: – methylergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1 mL ampoule.
misoprostol	**Tablet:** 200 micrograms. – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used. **Vaginal tablet:** 25 micrograms.* * Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1 mL.

22.4 Medicines for medical abortion

mifepristone – misoprostol	**Tablet** 200 mg – **tablet** 200 micrograms. **Co-package containing:** mifepristone 200 mg tablet [1] and misoprostol 200 micrograms tablet [4]. – Management of intrauterine fetal demise – Management of induced abortion
misoprostol	**Tablet:** 200 micrograms. – Management of incomplete abortion and miscarriage

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.5 Antioxytocics (tocolytics)

nifedipine	**Immediate-release capsule:** 10 mg.

22.6 Other medicines administered to the mother

dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule.	
multiple micronutrient supplement*	**Tablet containing:**	
	Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent
	Vitamin C (ascorbic acid)	70 mg
	Vitamin D (cholecalciferol)	5 micrograms (200 IU)
	Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent
	Vitamin B1 (thiamine mononitrate)	1.4 mg
	Vitamin B2 (riboflavin)	1.4 mg
	Vitamin B3 (niacinamide)	18 mg niacin equivalent
	Vitamin B6 (pyridoxine hydrochloride)	1.9 mg
	Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)
	Vitamin B12 (cyanocobalamin)	2.6 micrograms
	Iron (ferrous fumarate)	30 mg
	Iodine (potassium iodide)	150 micrograms
	Zinc (zinc oxide)	15 mg
	Selenium (sodium selenite)	65 micrograms
	Copper (cupric oxide)	2 mg
	* For use in specific contexts. Refer to current WHO recommendations.	
tranexamic acid	**Injection:** 100 mg/mL in 10 mL ampoule.	

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.7 Medicines administered to the neonate [c]

caffeine citrate [c]	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). **Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine [c]	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

Complementary List

☐ *alprostadil (prostaglandin E1) [c]* *Therapeutic alternatives:* – *dinoprostone (prostaglandin E2)*	***Solution for injection:** 0.5 mg/mL in alcohol.*
beractant [c]	***Suspension for intratracheal instillation:** 25 mg/mL.*
☐ *ibuprofen [c]* *Therapeutic alternatives:* – *indometacin*	***Solution for injection:** 5 mg/mL.*
poractant alfa [c]	***Suspension for intratracheal instillation:** 80 mg/mL.*

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution	***Solution:** of appropriate composition in accordance with local clinical guidelines.*

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines for psychotic disorders

☐ fluphenazine Therapeutic alternatives: – haloperidol decanonate – zuclopenthixol decanonate	**Injection:** 25 mg (decanoate or enantate) in 1 mL ampoule.
☐ haloperidol Therapeutic alternatives: – chlorpromazine	**Tablet:** 2 mg; 5 mg.
haloperidol	**Injection:** 5 mg/mL in 1 mL ampoule.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*	
olanzapine	**Powder for injection:** 10 mg in vial.
☐ paliperidone Therapeutic alternatives: – aripiprazole once-monthly injection – risperidone injection	**Injection (prolonged-release):** 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe.
☐ risperidone Therapeutic alternatives: – aripiprazole – olanzapine – paliperidone – quetiapine	**Solid oral dosage form:** 0.25 mg to 6.0 mg.
Complementary List	
clozapine	***Solid oral dosage form:*** *25 to 200 mg.*
24.2 Medicines for mood disorders	
24.2.1 ***Medicines for depressive disorders***	
amitriptyline	**Tablet:** 25 mg; 75mg (hydrochloride).
☐ fluoxetine Therapeutic alternatives: – citalopram – escitalopram – fluvoxamine – paroxetine – sertraline	**Solid oral dosage form:** 20 mg (as hydrochloride).
24.2.2 ***Medicines for bipolar disorders***	
carbamazepine	**Tablet (scored):** 100 mg; 200 mg; 400 mg.
lithium carbonate	**Solid oral dosage form:** 300 mg.
☐ quetiapine Therapeutic alternatives: – aripiprazole – olanzapine – paliperidone	**Tablet (immediate-release):** 25 mg; 100 mg; 150 mg; 200 mg; 300 mg. **Tablet (modified-release):** 50 mg; 150 mg; 200 mg; 300 mg; 400 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

valproic acid (sodium valproate)*	**Tablet (enteric-coated):** 200 mg; 500 mg.

* *Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*

24.3 Medicines for anxiety disorders

☐ diazepam*	**Tablet (scored):** 2 mg; 5 mg.
Therapeutic alternatives: – lorazepam	* For short-term emergency management of acute and severe anxiety symptoms only.
☐ fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
Therapeutic alternatives: – citalopram – escitalopram – fluvoxamine – paroxetine – sertraline	

24.4 Medicines for obsessive compulsive disorders

clomipramine	**Capsule:** 10 mg; 25 mg (hydrochloride).
☐ fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
Therapeutic alternatives: – citalopram – escitalopram – fluvoxamine – paroxetine – sertraline	

24.5 Medicines for disorders due to psychoactive substance use

24.5.1 ***Medicines for alcohol use disorders***

acamprosate calcium	**Tablet:** 333 mg.
naltrexone	**Injection suspension (extended-release):** 380 mg in vial. **Tablet:** 50 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

24.5.2 *Medicines for nicotine use disorders*

bupropion	**Tablet (sustained-release):** 150 mg (hydrochloride).
cytisine (cytisinicline)	**Tablet:** 1.5 mg.
nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). **Lozenge:** 2 mg; 4 mg. **Oral spray:** 1 mg per actuation. **Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
varenicline	**Tablet:** 0.5 mg; 1 mg.

24.5.3 *Medicines for opioid use disorders*

Complementary List

☐ *methadone** *Therapeutic alternatives:* – *buprenorphine*	***Concentrate for oral liquid:*** *5 mg/mL; 10 mg/mL (hydrochloride).* ***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL (hydrochloride).*

* *The medicines should only be used within an established support programme.*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease

☐ budesonide Therapeutic alternatives: – beclometasone – ciclesonide – fluticasone – mometasone	**Powder for inhalation:** 100 micrograms per actuation; 200 micrograms per actuation in dry powder inhaler. **Suspension for inhalation:** 100 micrograms per actuation; 200 micrograms per actuation in pressurized metered-dose inhaler.
☐ budesonide + ☐ formoterol Therapeutic alternatives: – beclometasone + formoterol – budesonide + salmeterol – fluticasone + formoterol – fluticasone furoate + vilanterol – mometasone + formoterol	**Powder for inhalation:** 100 micrograms + 6 micrograms per actuation; 200 micrograms + 6 micrograms per actuation in dry powder inhaler.

25. MEDICINES ACTING ON THE RESPIRATORY TRACT *(continued)*	
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
ipratropium bromide	**Solution for inhalation:** 20 micrograms per actuation in pressurized metered-dose inhaler.
☐ salbutamol Therapeutic alternatives: – terbutaline	**Inhalation:** 500 micrograms/mL (as sulfate) in 1 mL, 5 mL ampoule. **Solution for inhalation:** 100 micrograms (as sulfate) per actuation in pressurized metered-dose inhaler; 2.5 mg/2.5 mL; 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multi-dose bottle for use in nebulizers.
☐ tiotropium Therapeutic alternatives: – aclidinium – glycopyrronium – umeclidinium	**Powder for inhalaton:** 18 micrograms in capsule. **Solution for inhalation:** 1.25 micrograms; 2.5 micrograms per actuation in soft mist inhaler.
26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES	
26.1 Oral	
oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**
26.2 Parenteral	
glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/L, Cl^- 30 mmol/L). **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na^+ 150 mmol/L and Cl^- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na^+ 75 mmol/L and Cl^- 75 mmol/L) [c] .

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES *(continued)*	
potassium chloride	**Solution:** 11.2% in 20 mL ampoule (equivalent to K^+ 1.5 mmol/mL, Cl^- 1.5 mmol/mL). **Solution for dilution:** 7.5% (equivalent to K^+ 1 mmol/mL and Cl^- 1 mmol/mL) [c]; 15% (equivalent to K^+ 2 mmol/mL and Cl^- 2 mmol/mL) [c].
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na^+ 154 mmol/L, Cl^- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na^+ 167 mmol/L, HCO_3^- 167 mmol/L). **Solution:** 8.4% in 10 mL ampoule (equivalent to Na^+ 1000 mmol/L, HCO_3^- 1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**
26.3 Miscellaneous	
water for injection	2 mL; 5 mL; 10 mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
calcium	**Tablet:** 500 mg (elemental).
☐ colecalciferol [c] Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
☐ ergocalciferol Therapeutic alternatives: – colecalciferol	**Oral liquid:** 250 micrograms/mL (10 000 IU/mL). **Solid oral dosage form:** 1.25 mg (50 000 IU).
iodine	**Iodized oil:** 480 mg iodine/mL in 10 mL ampoule or vial (oral or injectable).
multiple micronutrient powder [c]	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values

27. VITAMINS AND MINERALS *(continued)*	
nicotinamide	**Tablet:** 50 mg.
pyridoxine	**Tablet:** 10 mg [c]; 25 mg (hydrochloride).
retinol	**Soft capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as acetate or palmitate). **Oral liquid:** 100 000 IU/mL (as palmitate). **Water-miscible injection:** 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial.
riboflavin	**Tablet:** 5 mg.
thiamine	**Injection:** 50 mg/mL (hydrochloride) in ampoule or vial [c]. **Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:*** *100 mg/mL in 10 mL ampoule.*
28. EAR, NOSE AND THROAT MEDICINES	
acetic acid [c]	**Solution (ear drops):** 2%.
☐ budesonide [c] Therapeutic alternatives to be reviewed	**Nasal spray:** 32 micrograms; 64 micrograms per actuation.
☐ ciprofloxacin [c] Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline [c] Therapeutic alternatives to be reviewed	**Nasal drops:** 0.05%. **Nasal spray:** 0.05%.
29. MEDICINES FOR DISEASES OF JOINTS	
29.1 Medicines used to treat gout	
allopurinol	**Tablet:** 100 mg.
29.2 Disease-modifying anti-rheumatic drugs (DMARDs)	
chloroquine	**Tablet:** 100 mg; 150 mg (as phosphate or sulfate).

29. MEDICINES FOR DISEASES OF JOINTS *(continued)*

Complementary List

azathioprine	***Tablet:*** *50 mg.*
hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium).*
penicillamine	***Solid oral dosage form:*** *250 mg.*
sulfasalazine	***Tablet:*** *500 mg.*

29.3 Medicines for juvenile joint diseases

Complementary List

*acetylsalicylic acid**	***Suppository:*** *150 mg; 300 mg.* ***Tablet:*** *100 mg to 500 mg.* ***Tablet (dispersible):*** *75 mg; 300 mg; 500 mg.* ** For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*
☐ *adalimumab** *Therapeutic alternatives:* – *certolizumab pegol* – *etanercept* – *golimumab* – *infliximab* ** including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL [c] ; 20 mg/0.2 mL [c] ; 20 mg/0.4 mL [c] ; 40 mg/0.4 mL; 40 mg/0.8 mL; 80 mg/0.8 mL in pre-filled syringe or pre-filled pen.*
methotrexate	***Tablet:*** *2.5 mg (as sodium).*
☐ *triamcinolone hexacetonide* *Therapeutic alternatives:* – *triamcinolone acetonide*	***Injection:*** *20 mg/mL in vial.*

30. DENTAL MEDICINES AND PREPARATIONS

fluoride	**Gel:** containing 2500 to 12 500 ppm fluoride (any type). **Mouthrinse:** containing 230 to 900 ppm fluoride (any type). **Toothpaste, cream or gel:** containing 1000 to 1500 ppm fluoride (any type). **Varnish:** containing 22 500 ppm fluoride (any type).

30. DENTAL MEDICINES AND PREPARATIONS *(continued)*	
glass ionomer cement	**Single-use capsules:** 0.4 g powder + 0.09 mL liquid. **Multi-use bottle:** powder + liquid. Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
resin-based composite (low-viscosity)*	**Single-use applicator or multi-use bottle** * of any type for use as dental sealant.
resin-based composite (high-viscosity)*	**Single-use capsule or multi-use syringe** * of any type for use as dental filling material
silver diamine fluoride	**Solution:** 38% w/v.

Table 1: Explanation of dosage forms

A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability. The term 'solid oral dosage form' is never intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is never intended to allow any type of modified-release tablet.
Tablets (qualified)	Refers to a specific type of tablet: **chewable** - tablets that are intended to be chewed before being swallowed; **dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** - tablets that are intended to be crushed before being swallowed; **scored** - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; **sublingual** - tablets that are intended to be placed beneath the tongue.

* Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

Table 1 *continued*

Term	Definition
	The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Capsules	Refers to hard or soft capsules. The term 'capsule' without qualification is *never* intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid. The term 'granules' without further qualification is never intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but *not* those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes. Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

Table 1 *continued*

B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term 'injection' is qualified by '(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, solution for inhalation, suspension for inhalation.

Annex 2

WHO Model List of Essential Medicines for Children – 10th List (2025)

Explanatory notes

This Model List is intended for use for children up to and including 12 years of age.

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost–effectiveness in a variety of settings. Medicines on the complementary list are presented in italics.

The **square box symbol** (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 24th WHO Model List of Essential Medicines is used for the 10th WHO Model Essential List for Children. Some sections have been deleted because they contain medicines that are not relevant for children.

The [a] symbol indicates that there is an age or weight restriction on use of the medicine.

The presence of an entry on the Essential Medicines List for Children carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

isoflurane	**Inhalation.**
nitrous oxide*	**Inhalation.** * Piped nitrous oxide is a major source of atmospheric pollution from healthcare facilities. Point-of-care cylinders are the preferred delivery system over centrally-supplied (piped) delivery systems.
oxygen	**Inhalation** (medical gas).
sevoflurane	**Inhalation.**

1.1.2 *Injectable medicines*

ketamine	**Injection:** 10 mg/mL; 50 mg/mL (as hydrochloride) in vial.
☐ propofol Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed	**Injection:** 0.25%; 0.5% (hydrochloride). **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule in 8% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed	**Injection:** 0.5%; 1%; 2% (hydrochloride). **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule in 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000.

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 400 micrograms/mL;1 mg/mL (sulfate) in 1mL ampoule or vial.
☐ midazolam Therapeutic alternatives to be reviewed	**Injection:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. **Oral liquid:** 2 mg/mL.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*	
morphine	**Injection**: 1 mg/mL; 2 mg/mL; 10 mg/mL (sulfate or hydrochloride) in 1 mL ampoule.
1.4 Medical gases	
oxygen*	**Inhalation.** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.
2. MEDICINES FOR PAIN AND PALLIATIVE CARE	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
ibuprofen [a]	**Oral liquid:** 100 mg/5 mL; 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol (acetaminophen)*	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL**; 250 mg/5 mL. **The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 100 mg; 250 mg. **Tablet:** 250 mg; 325 mg; 500 mg. **Tablet (dispersible):** 100 mg; 250 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
2.2 Opioid analgesics	
☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg; 30 mg; 60 mg; 100 mg (morphine sulfate). **Injection:** 1 mg/mL; 2 mg/mL; 10 mg/mL (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 5 mg/5 mL;10 mg/5 mL (morphine hydrochloride or morphine sulfate). **Solid oral dosage form (slow release):** 5 mg;10 mg; 30 mg; 60 mg; 100 mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
Complementary list	
*methadone**	***Tablet:*** *5 mg (hydrochloride).* ***Oral liquid:*** *5 mg/5 mL (hydrochloride).* ***Concentrate for oral liquid:*** *25 mg/5 mL (hydrochloride)* * *For the management of cancer pain.*
2.3 Medicines for other common symptoms in palliative care	
amitriptyline	**Oral liquid:** 25 mg/5 mL. **Tablet:** 10 mg; 25 mg.
cyclizine	**Injection:** 50 mg/mL (lactate). **Tablet:** 50 mg (hydrochloride).
dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL, 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg, 0.75 mg, 1.5 mg, 2 mg, 4 mg (as dexamethasone base).
diazepam	**Oral liquid:** 2 mg/5 mL. **Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube. **Tablet (scored):** 2 mg; 5 mg; 10 mg.
docusate sodium	**Oral liquid:** 12.5 mg/5 mL; 50 mg/5 mL.
hyoscine hydrobromide	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches**: 1 mg/72 hours.
lactulose	**Oral liquid:** 3.3 to 3.4 g/5 mL.
midazolam	**Injection*:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL, 3 mL vial. * May be used for buccal administration when solution for oromucosal administration is not available. **Oral liquid:** 2mg/mL. **Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL prefilled syringe.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*	
☐ ondansetron Therapeutic alternatives – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg/mL in 2 mL, 4 mL ampoule (as hydrochloride dihydrate). **Oral liquid:** 4 mg/5 mL (as hydrochloride dihydrate). **Solid oral dosage form:** 4 mg; 8 mg (as hydrochloride dihydrate).
senna	**Oral liquid:** 7.5 mg/5 mL.
3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS	
dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg; 0.75 mg; 1.5 mg; 2 mg; 4 mg (as dexamethasone base).
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.
☐ loratadine* Therapeutic alternatives: – cetirizine – fexofenadine	**Oral liquid:** 1 mg/mL. **Tablet:** 10 mg. **Tablet (chewable):** 5 mg; 10 mg. * There may be a role for sedating antihistamines for limited indications.
☐ prednisolone Therapeutic alternatives: – prednisone	**Oral liquid:** 5 mg/mL. **Tablet:** 5 mg; 25 mg.
4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS	
4.1 Non-specific	
charcoal, activated	**Granules for oral suspension*:** 50 mg. * Alternative formulations of activated charcoal may be used if granules are not available.
4.2 Specific	
acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*	
atropine	**Injection:** 1 mg/mL (sulfate) in 1 mL ampoule or vial.
calcium gluconate	**Injection:** 100 mg/mL (10%) in 10 mL ampoule or vial.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.
Complementary List	
deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*
dimercaprol	***Injection in oil:*** *50 mg/mL in 2 mL ampoule; 100 mg/mL in 3 mL ampoule.*
fomepizole	***Injection:*** *5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule or vial.*
sodium calcium edetate	***Injection:*** *200 mg/mL in 5 mL ampoule.*
succimer	***Solid oral dosage form:*** *100 mg.*

5. MEDICINES FOR NEUROLOGICAL DISORDERS	
5.1 Medicines for central nervous system disorders	
5.1.1 ***Inhalational medicines***	
carbamazepine	**Oral liquid:** 100 mg/5 mL. **Tablet (chewable):** 100 mg; 200 mg. **Tablet (scored):** 100 mg; 200 mg; 400 mg.
diazepam	**Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg. **Tablet (chewable, dispersible):** 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. * For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
levetiracetam	**Oral liquid:** 100 mg/mL. **Tablet:** 250 mg; 500 mg; 750 mg; 1000 mg.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*	
midazolam	**Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe. **Injection*:** 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial. * For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 30 mg/mL or 60 mg/mL; 200 mg/mL (sodium). **Oral liquid:** 15 mg/5 mL. **Tablet:** 15 mg; 30 mg; 60 mg; 100 mg.
phenytoin	**Injection:** 50 mg/mL (phenytoin sodium). **Oral liquid:** 30 mg/5 mL (phenytoin). **Solid oral dosage form:** 25 mg; 50 mg; 100 mg (phenytoin sodium). **Tablet (chewable):** 50 mg (phenytoin).
prednisolone	**Oral liquid:** 1 mg/mL. **Tablet:** 1 mg, 5 mg, 10 mg.
valproic acid (sodium valproate)* * *Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*	**Oral liquid:** 200 mg/5 mL. **Tablet (crushable):** 100 mg. **Tablet (enteric-coated):** 200 mg; 500 mg.
Complementary List	
ethosuximide	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.*
levetiracetam	***Concentrate solution for infusion:*** *100 mg/mL in 5 mL ampoule or vial.* ***Solution for infusion:*** *5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.*

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

*valproic acid (sodium valproate)**	***Injection:*** *100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*

* *Valproic acid (sodium valproate) is not recommended in women and girls of childbearing potential owing to the high risk of birth defects and neurodevelopmental disorders in children exposed to valproic acid (sodium valproate) in the womb.*

~~5.1.2 *Medicines for multiple sclerosis*~~

~~5.1.3 *Medicines for parkinsonism*~~

5.1.4 *Medicines for cerebral palsy*

Complementary List

baclofen	***Intrathecal injection:*** *500 micrograms/mL in ampoule.* ***Oral liquid:*** *10 mg/5 mL.* ***Tablet:*** *10 mg.*

5.1.5 *Medicines for headache disorders*

5.1.5.1 *Medicines for acute migraine attacks*

ibuprofen	**Oral liquid:** 100 mg/5 mL. **Tablet:** 200 mg; 400 mg.
paracetamol (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL. * The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 250 mg. **Tablet:** 250 mg; 325 mg; 500 mg. **Tablet (dispersible):** 100 mg; 250 mg.

5.1.5.2 *Medicines for migraine prophylaxis*

propranolol	**Tablet:** 10 mg; 40 mg (hydrochloride).

~~5.1.5.3 *Medicines for cluster headache*~~

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

5.1.6 *Medicines for central nervous system infections*

5.1.6.1 *Medicines for bacterial central nervous system infections*

amoxicillin

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate).

Solid oral dosage form: 250 mg; 500 mg (as trihydrate).

Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	

ceftriaxone* [a]

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

chloramphenicol

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.

Powder for injection: 1 g (sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates*	

Complementary List

*meropenem** [a]

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*

[a] > 3 months.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis in neonates*

5.1.6.2 ***Medicines for viral central nervous system infections***

☐ aciclovir

Oral liquid: 200 mg/5 mL.

Powder for solution for infusion: 250 mg (as sodium dihydrate) in vial.

Solution for infusion: 25 mg/mL (as sodium) in vial.

Tablet: 200 mg.

5.2 Medicines for peripheral nervous system disorders

5.2.1 ***Medicines for Guillain-Barré syndrome***

Complementary List

normal immunoglobulin

Intravenous administration: *5%; 10% protein solution.*

5.2.2 ***Medicines for myasthenia gravis***

neostigmine

Injection: 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.

5. MEDICINES FOR NEUROLOGICAL DISORDERS *(continued)*

Complementary List

pyridostigmine	***Injection:*** *5 mg/mL (bromide) in ampoule or vial.* ***Tablet (scored):*** *60 mg (bromide).*

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

albendazole	**Tablet (chewable, scored):** 400 mg.
ivermectin	**Tablet:** 3 mg.
levamisole	**Tablet:** 50 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 500 mg. **Tablet (scored):** 600 mg.
pyrantel	**Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 *Antifilarials*

albendazole	**Tablet (chewable, scored):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
☐ ivermectin	**Tablet:** 3 mg.

Therapeutic alternatives:
- moxidectin

6.1.3 *Antischistosomals and other antitrematode medicines*

☐ praziquantel*	**Tablet:** 150 mg, 500 mg.
Therapeutic alternatives: – arpraziquantel (Tablet (dispersible): 150 mg).	**Tablet (scored):** 600 mg.
* The square box applies only to the listing of praziquantel on the EMLc for schistosomiasis	
triclabendazole	**Tablet (scored):** 250 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
Complementary List	
*oxamniquine**	***Capsule:*** *250 mg.* ***Oral liquid:*** *250 mg/5 mL.* * *For use when praziquantel treatment fails.*
6.1.4 ***Cysticidal medicines***	
Complementary List	
albendazole	***Tablet (chewable):*** *200 mg.* ***Tablet (chewable, scored):*** *400 mg.*
mebendazole	***Tablet (chewable)****: 100 mg, 500 mg.*
praziquantel	***Tablet:*** *150 mg, 500 mg.* ***Tablet (scored)****: 600 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programmes involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 *Access group antibiotics*

amikacin

Injection: 50 mg/mL (as sulfate); 250 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
- *High-risk febrile neutropenia* - *Pyelonephritis (severe)*	- *Sepsis in neonates and children*

amoxicillin

Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate).

Solid oral dosage form: 250 mg; 500 mg; (as trihydrate).

Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
- *Community acquired pneumonia (mild to moderate)* - *Community acquired pneumonia (severe)* - *Complicated severe acute malnutrition* - *Otitis media* - *Pharyngitis* - *Progressive apical dental abscess* - *Sepsis in neonates and children* - *Sinusitis* - *Uncomplicated severe acute malnutrition*	- *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid

Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.

Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL.

Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt).

Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt); 250 mg (as trihydrate) + 62.5 mg (as potassium salt).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Hospital acquired pneumonia* – *Low-risk febrile neutropenia* – *Lower urinary tract infections* – *Sinusitis* – *Skin and soft tissue infections*	– *Bone and joint infections* – *Community-acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* – *Otitis media* – *Surgical prophylaxis*

ampicillin

Powder for injection: 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children*	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin

Powder for injection: 1.2 million IU (≈ 900 mg) in vial; 2.4 million IU (≈ 1.8 g) in vial.

FIRST CHOICE	SECOND CHOICE
– *Syphilis (congenital)*	

benzylpenicillin

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children* – *Syphilis (congenital)*	– *Acute bacterial meningitis*

cefalexin

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous).

Solid oral dosage form: 250 mg (as monohydrate).

Tablet (dispersible): 125 mg; 250 mg.

FIRST CHOICE	SECOND CHOICE
– *Skin and soft tissue infections*	– *Pharyngitis*

cefazolin [a]

Powder for injection: 1 g (as sodium salt) in vial.

[a] > 1 month.

FIRST CHOICE	SECOND CHOICE
– *Surgical prophylaxis*	– *Bone and joint infections*

chloramphenicol

Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule.

* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.

Powder for injection: 1 g (as sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg/mL (as phosphate).

Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Necrotizing fasciitis*	– *Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:

– 4th level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 250 mg, 500 mg; 1 g (as sodium).

Powder for injection: 250 mg, 500 mg (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL, 250 mg/5 mL (as sodium).

* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– *Bone and joint infections* – *Skin and soft tissue infections*	– *Sepsis in neonates and children*

doxycycline [a]

Oral liquid: 50 mg/5 mL (calcium).

Powder for oral liquid: 25 mg/5 mL (monohydrate).

Powder for injection: 100 mg in vial.

Solid oral dosage form: 50 mg; 100 mg (as hyclate).

Tablet (dispersible): 100 mg (as monohydrate).

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
	– *Cholera* – *Community acquired pneumonia (mild to moderate)*

6. ANTI-INFECTIVE MEDICINES *(continued)*

gentamicin

Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis in neonates* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections* – *Complicated severe acute malnutrition* – *Sepsis in neonates and children*	– *Surgical prophylaxis*

metronidazole

Injection: 500 mg in 100 mL vial.

Oral liquid: 200 mg/5 mL (as benzoate).

Tablet: 200 mg; 250 mg; 400 mg; 500 mg.

FIRST CHOICE	SECOND CHOICE
– *C. difficile infection* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Necrotizing fasciitis* – *Surgical prophylaxis*	– *Complicated intraabdominal infections (mild to moderate)*

nitrofurantoin

Oral liquid: 25 mg/5 mL.

Solid oral dosage form: 50 mg; 100 mg.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg/5 mL (as potassium). **Solid oral dosage form:** 250 mg; 500 mg (as potassium).	
	FIRST CHOICE – *Community acquired pneumonia (mild to moderate)* – *Pharyngitis* – *Progressive apical dental abscess*	**SECOND CHOICE**
procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	FIRST CHOICE – *Syphilis (congenital)*	**SECOND CHOICE**
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg. **Tablet (dispersible):** 100 mg + 20 mg.	
	FIRST CHOICE – *Lower urinary tract infections*	**SECOND CHOICE** – *Acute invasive bacterial diarrhoea / dysentery*
trimethoprim	**Tablet:** 100 mg; 200 mg. **Oral liquid:** 50 mg/5 mL.	
	FIRST CHOICE – *Lower urinary tract infections*	**SECOND CHOICE**

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 ***Watch group antibiotics***

azithromycin

Solid oral dosage form: 250 mg; 500 mg (anhydrous).

Powder for oral liquid: 200 mg/5 mL (anhydrous).

FIRST CHOICE	SECOND CHOICE
– *Cholera* – *Enteric fever* – *Trachoma* – *Yaws*	– *Acute invasive bacterial diarrhoea / dysentery*

cefixime

Powder for oral liquid: 100 mg/5 mL.

Solid oral dosage form: 200 mg; 400 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute invasive bacterial diarrhoea / dysentery*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intraabdominal infections (severe)* – *Hospital acquired pneumonia* – *Pyelonephritis (severe)*	– *Bone and joint infections* – *Pyelonephritis (mild to moderate)* – *Sepsis in neonates and children*

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis* – *Community acquired pneumonia (severe)* – *Complicated intraabdominal infections (mild to moderate)* – *Complicated intrabdominal infections (severe)* – *Endophthalmitis* – *Enteric fever* – *Hospital acquired pneumonia* – *Necrotizing fasciitis* – *Pyelonephritis (severe)*	– *Acute invasive bacterial diarrhoea / dysentery* – *Bone and joint infections* – *Pyelonephritis (mild to moderate)* – *Sepsis in neonates and children*

cefuroxime

Powder for injection: 250 mg; 750 mg; 1.5 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Surgical prophylaxis*

ciprofloxacin

Oral liquid: 250 mg/5 mL (anhydrous).

Solution for IV infusion: 2 mg/mL (as hyclate).

Solid oral dosage form: 100 mg; 250 mg; (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Acute invasive bacterial diarrhoea / dysentery* – *Enteric fever* – *Low-risk febrile neutropenia* – *Pyelonephritis (mild to moderate)*	– *Cholera* – *Complicated intraabdominal infections (mild to moderate)*

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ clarithromycin

Therapeutic alternatives:

– erythromycin

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL.

Powder for injection: 500 mg in vial.

Solid oral dosage form: 250 mg.

FIRST CHOICE	SECOND CHOICE
	– *Pharyngitis*

piperacillin + tazobactam

Powder for injection: 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia* – *Hospital acquired pneumonia* – *Necrotizing fasciitis*	

vancomycin*

Capsule: 125 mg; 250 mg (as hydrochloride).

* vancomycin powder for injection may also be used for oral administration

FIRST CHOICE	SECOND CHOICE
	– *C. difficile infection*

Complementary List

ceftazidime

Powder for injection: *250 mg; 1 g (as pentahydrate) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ *meropenem** [a]

Therapeutic alternatives:*

– *imipenem + cilastatin*

* *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*

[a] > 3 months.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis in neonates* – *Complicated intraabdominal infections (severe)* – *High-risk febrile neutropenia*

vancomycin

Powder for injection: *250 mg; 500 mg; 1 g (as hydrochloride) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis* – *Necrotizing fasciitis*	– *High-risk febrile neutropenia*

6.2.3 ***Reserve group antibiotics***

Complementary List

ceftazidime + avibactam	***Powder for injection:*** *2 g + 0.5 g in vial.*
ceftolozane + tazobactam	***Powder for injection:*** *1 g + 0.5 g in vial.*
colistin	***Powder for injection:*** *1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial.*
fosfomycin	***Powder for injection:*** *2 g; 4 g (as sodium) in vial.*
☐ *linezolid*	***Injection for intravenous administration:*** *2 mg/mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet (dispersible):*** *150 mg.*
polymyxin B	***Powder for injection:*** *500 000 IU (equivalent to 50 mg polymyxin B base) in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.4 *Antileprosy medicines*

Medicines used in the treatment of leprosy must be used in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.

6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

amikacin	**Injection:** 250 mg/mL (as sulfate) in 2 mL vial.
amoxicillin + clavulanic acid*	**Powder for oral liquid:** 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL. **Tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt). **Tablet (dispersible):** 250 mg (as trihydrate) + 62.5 mg (as potassium salt). * For use only in combination with meropenem.
bedaquiline	**Tablet:** 20 mg; 100 mg.
clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
cycloserine	**Solid oral dosage form:** 125 mg; 250 mg.
delamanid	**Tablet (dispersible):** 25 mg. **Tablet:** 50 mg.
ethambutol	**Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg.
☐ ethionamide	**Tablet:** 250 mg.
Therapeutic alternatives*: – protionamide * for multidrug-resistant tuberculosis	**Tablet (dispersible):** 125 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
isoniazid	**Tablet:** 100 mg; 300 mg. **Tablet (dispersible, scored):** 100 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	**Tablet (dispersible):** 50 mg + 75 mg.
isoniazid + rifapentine	**Tablet (scored):** 300 mg + 300 mg.
levofloxacin	**Tablet:** 250mg; 500 mg. **Tablet (dispersible):** 100 mg.
linezolid	**Tablet:** 600 mg. **Tablet (dispersible, scored):** 150 mg.
meropenem	**Powder for injection:** 500 mg (as trihydrate); 1 g (as trihydrate) in vial.
moxifloxacin	**Tablet:** 400 mg. **Tablet (dispersible):** 100 mg.
p-aminosalicylate sodium	**Powder for oral solution:** 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid).
pyrazinamide	**Tablet:** 400 mg; 500 mg. **Tablet (dispersible):** 150 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine	**Tablet:** 150 mg; 300 mg. **Tablet (dispersible, scored):** 150 mg.
streptomycin	**Powder for injection:** 1 g (as sulfate) in vial.
6.3 Antifungal medicines	
amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial. **Powder for injection:** 50 mg (as sodium deoxycholate) in vial. * Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
fluconazole	**Capsule:** 50 mg. **Injection:** 2 mg/mL in vial. **Oral liquid:** 50 mg/5 mL. **Powder for oral liquid:** 50 mg/5 mL.
flucytosine	**Capsule:** 250 mg. **Infusion:** 2.5 g in 250 mL.
griseofulvin	**Oral liquid:** 125 mg/5 mL. **Solid oral dosage form:** 125 mg; 250 mg.
itraconazole*	**Capsule:** 100 mg. **Oral liquid:** 10 mg/mL. * For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.
nystatin	**Lozenge:** 100 000 IU. **Oral liquid:** 100 000 IU/mL. **Solid oral dosage form:** 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg. **Powder for injection:** 200 mg in vial. **Powder for oral liquid:** 40 mg/mL. * For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.
Complementary List	
☐ *micafungin* *Therapeutic alternatives:* – *anidulafungin* – *caspofungin*	***Powder for injection:*** *50 mg (as sodium); 100 mg (as sodium) in vial.*
potassium iodide	***Saturated solution.***

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

aciclovir	**Oral liquid:** 200 mg/5 mL. **Powder for solution for infusion:** 250 mg (as sodium dihydrate) in vial. **Solution for infusion:** 25 mg/mL (as sodium) in vial. **Tablet:** 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

lamivudine	**Oral liquid:** 50 mg/5 mL.
zidovudine	**Oral liquid:** 50 mg/5 mL.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

nevirapine [a]	**Oral liquid:** 50 mg/5 mL. **Tablet (dispersible):** 50 mg. [a] > 6 weeks

6.4.2.3 *Protease inhibitors*

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

darunavir [a]	**Tablet:** 75 mg. [a] > 3 years

6. ANTI-INFECTIVE MEDICINES *(continued)*

lopinavir + ritonavir	**Solid oral dosage form:** 40 mg + 10 mg. **Tablet (heat stable):** 100 mg + 25 mg.
ritonavir	**Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 ***Integrase inhibitors***

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg. [a] ≥ 4 weeks and ≥ 3 kg **Tablet:** 50 mg. [a] ≥ 25 kg
raltegravir*	**Granules for oral suspension:** 100 mg in sachet. * For use in second-line regimens in accordance with WHO treatment guidelines.

6.4.2.5 ***Fixed-dose combinations of antiretroviral medicines***

abacavir + dolutegravir + lamivudine	**Tablet (dispersible, scored):** 60 mg (as sulfate) + 5 mg + 30 mg.
abacavir + lamivudine	**Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg.

6.4.2.6 ***Medicines for prevention of HIV-related opportunistic infections***

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6.4.3 ***Other antivirals***

Complementary list

*oseltamivir**	***Capsule:*** *30 mg; 45 mg; 75 mg (as phosphate).* ***Powder for oral liquid:*** *6 mg/mL (as phosphate).* * *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
*valganciclovir**	***Powder for oral solution:*** *50 mg/mL (as hydrochloride).* ***Tablet:*** *450 mg (as hydrochloride).* * *For the treatment of cytomegalovirus retinitis (CMVr).*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4 Antihepatitis medicines

6.4.4.1 *Medicines for hepatitis B*

6.4.4.1.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

entecavir	**Oral liquid:** 0.05 mg/mL. **Tablet:** 0.5 mg; 1 mg.

6.4.4.2 *Medicines for hepatitis C*

Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.

6.4.4.2.1 ☐ *Pangenotypic direct-acting antiviral combinations*

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride). * Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg (as dihydrochloride) + 400 mg.
glecaprevir + pibrentasvir	**Granules:** 50 mg + 20 mg in sachet. **Tablet:** 100 mg + 40 mg.
sofosbuvir*	**Granules:** 200 mg in sachet. **Tablet:** 200 mg; 400 mg. * Pangenotypic when used in combination with daclatasvir
sofosbuvir + velpatasvir	**Granules:** 150 mg + 37.5 mg; 200 mg + 50 mg in sachet [c]. **Tablet:** 200 mg + 50 mg; 400 mg + 100 mg.

~~*6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations*~~

~~*6.4.4.2.3 Other antivirals for hepatitis C*~~

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide* [a] * proposed for deletion in 2027	**Tablet:** 500 mg (furoate). [a] > 25 kg.
☐ metronidazole Therapeutic alternatives: – tinidazole	**Injection:** 500 mg in 100 mL vial. **Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg; 250 mg; 400 mg; 500 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.2 ***Antileishmaniasis medicines***

amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial. **Powder for injection:** 50 mg (as sodium deoxycholate) in vial. * Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.
meglumine antimoniate	**Injection:** 1.5 g/5 mL in 5 mL ampoule.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	**Injection:** 100 mg/mL in 30 mL vial.

6.5.3 ***Antimalarial medicines***

6.5.3.1 ***Medicines for curative treatment***

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to WHO treatment guidelines for malaria.

artemether	**Oily injection:** 20 mg/mL; 40 mg/mL in 1 mL ampoule. For use in the management of severe malaria.
artemether + lumefantrine	**Tablet:** 20 mg + 120 mg. **Tablet (dispersible):** 20 mg + 120 mg.
artesunate	**Powder for injection:** 30 mg; 60 mg; 120 mg in vial. For use in the management of severe malaria. **Rectal dosage form:** 100 mg For pre-referral treatment of severe malaria only.
artesunate + amodiaquine	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.
artesunate + mefloquine	**Tablet:** 25 mg + 50 mg (as hydrochloride); 100 mg + 200 mg (as hydrochloride).
artesunate + pyronaridine	**Granules:** 20 mg + 60 mg (tetraphosphate). **Tablet:** 60 mg + 180 mg (tetraphosphate).
artesunate – sulfadoxine + pyrimethamine	**Co-packaged scored tablets:** artesunate 50 mg [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].

6. ANTI-INFECTIVE MEDICINES *(continued)*	
chloroquine*	**Oral liquid:** 50 mg/5 mL (base). **Tablet:** 150 mg (base). For use only in the treatment of *Plasmodium vivax* infection.
dihydroartemisinin + piperaquine	**Tablet:** 20 mg + 160 mg (phosphate); 40 mg + 320 mg (phosphate); 60 mg + 480 mg (phosphate); 80 mg + 640 mg (phosphate). **Tablet (dispersible):** 20 mg + 160 mg (phosphate); 40 mg + 320 mg (phosphate).
primaquine	**Tablet:** 7.5 mg; 15 mg (as phosphate). For use to reduce the transmission of *Plasmodium falciparum* and for radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections.
quinine	**Solution for infusion:** 60 mg/mL; 300 mg/mL (hydrochloride) in 2 mL ampoule. For use in the management of severe malaria.
6.5.3.2 ***Medicines for chemoprevention***	
amodiaquine – sulfadoxine + pyrimethamine	**Co-packaged dispersible tablets:** amodiaquine 75 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]. amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]. amodiaquine 150 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1]. amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
sulfadoxine + pyrimethamine	**Tablet (dispersible):** 250 mg + 12.5 mg.
6.5.3.3 ***Medicines for chemoprophylaxis in travellers***	
chloroquine	**Oral liquid:** 50 mg/5 mL (base). **Tablet:** 150 mg (base). For use only for prophylaxis of *Plasmodium vivax* infection.

6. ANTI-INFECTIVE MEDICINES *(continued)*

doxycycline [a]	**Oral liquid:** 50 mg/5 mL (calcium). **Powder for oral liquid:** 25 mg/5 mL (monohydrate). **Solid oral dosage form:** 50 mg; 100 mg (as hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). [a] > 8 years.
mefloquine [a]	**Tablet (scored):** 250 mg (as hydrochloride).

6.5.4 ***Antipneumocystosis and antitoxoplasmosis medicines***

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg. **Tablet (dispersible):** 100 mg + 20 mg.

6.5.5 ***Antitrypanosomal medicines***

6.5.5.1 ***African trypanosomiasis***

fexinidazole*	**Tablet:** 600 mg. * For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	**Powder for injection:** 300 mg (as isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg/mL (hydrochloride) in 50 mL bottle. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.

6. ANTI-INFECTIVE MEDICINES *(continued)*

nifurtimox*	**Tablet (scored):** 30 mg; 120 mg. * Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol	***Injection:*** *180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6.5.5.2 ***American trypanosomiasis***

benznidazole	**Tablet:** 12.5 mg. **Tablet (scored):** 50 mg; 100 mg.
nifurtimox	**Tablet (scored):** 30 mg; 120 mg.

6.6 Medicines for ectoparasitic infections

ivermectin	**Tablet:** 3 mg.

6.7 Medicines for Ebola virus disease

ansuvimab	**Powder for injection:** 400 mg
atoltivimab + maftivimab + odesivimab	**Injection:** 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial.

6.8 Medicines for COVID-19

WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.

Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.

The latest WHO Therapeutics and COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/nBkO1E

The latest WHO Drugs to prevent COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/L6RxYL

7. MEDICINES FOR CYSTIC FIBROSIS

elexacaftor + tezacaftor + ivacaftor	**Granules:** 80 mg + 40 mg + 60 mg; 100 mg + 50 mg + 75 mg in sachet. **Tablet:** 50 mg + 25 mg + 37.5 mg; 100 mg + 50 mg + 75 mg.
ivacaftor	**Granules:** 59.5 mg; 75 mg in sachet. **Tablet:** 75 mg; 150 mg.

Complementary List

pancreatic enzymes	***Capsule (modified release)*:*** *10 000 lipase units + 8000 amylase units + 600 protease units; 25 000 lipase units + 18 000 amylase units + 1000 protease units.* ** Units expressed in Ph.Eur*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Complementary List

☐ *adalimumab** *Therapeutic alternatives*:* – *etanercept* – *infliximab* ** including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL; 20 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.4 mL 40 mg/0.8 mL in pre-filled syringe or pre-filled pen.*
azathioprine	***Oral liquid:*** *10 mg/mL.* ***Powder for injection:*** *50 mg; 100 mg (as sodium salt) in vial.* ***Tablet:*** *25 mg.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/mL in 1 mL ampoule.* ***Oral liquid:*** *100 mg/mL.*
tacrolimus	***Capsule (immediate-release):*** *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.* ***Granules for oral supsension:*** *0.2 mg; 1 mg.* ***Injection:*** *5 mg/mL in 1 mL vial.*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide	***Concentrate for solution for infusion:*** *1 mg/mL; 2 mg/mL.* – *Acute promyelocytic leukaemia*
*asparaginase**	***Powder for injection:*** *10 000 IU in vial.* – *Acute lymphoblastic leukaemia*
bleomycin	***Powder for injection:*** *15 000 IU (as sulfate) in vial.* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Ovarian germ cell tumours* – *Testicular germ cell tumours*
calcium folinate (leucovorin calcium)	***Injection:*** *3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule.* ***Tablet:*** *5 mg; 15 mg; 25 mg.* – *Burkitt lymphoma* – *Osteosarcoma*
carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Retinoblastoma* – *Testicular germ cell tumours*
cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.* – *Low-grade glioma* – *Nasopharyngeal cancer* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Testicular germ cell tumours*

* *including quality-assured biosimilars*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* ***Solid oral dosage form:*** *25 mg, 50 mg.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
cytarabine	***Injection:*** *100 mg in vial.* ***Powder for injection:*** *100 mg in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Acute promyelocytic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Langerhans cell histiocytosis*
dacarbazine	***Powder for injection:*** *100 mg; 200 mg in vial.* – *Hodgkin lymphoma*
dactinomycin	***Powder for injection:*** *500 micrograms in vial.* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*
daunorubicin	***Injection:*** *2 mg/mL; 5 mg/mL (as hydrochloride) in vial.* ***Powder for injection:*** *20 mg; 50 mg (as hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia*
doxorubicin	***Injection:*** *2 mg/mL (hydrochloride) in vial.* ***Powder for injection:*** *10 mg; 50 mg (hydrochloride) in vial.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

doxorubicin (as pegylated liposomal)	***Injection:*** *2 mg/mL (hydrochloride) in 10 mL, 25 mL vial.* – *Kaposi sarcoma*
etoposide	***Capsule:*** *50 mg, 100 mg.* ***Injection:*** *20 mg/mL in 5 mL ampoule.* ***Powder for injection:*** *100 mg (as phosphate) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Retinoblastoma* – *Testicular germ cell tumours*
fluorouracil	***Injection:*** *50 mg/mL in vial.* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*
hydroxyurea (hydroxycarbamide)	***Solid oral dosage form:*** *100 mg; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.* – *Chronic myeloid leukaemia*
ifosfamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Rhabdomyosarcoma* – *Testicular germ cell tumours*
irinotecan	***Injection:*** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.* – *Metastatic colorectal cancer* – *Nephroblastoma (Wilms tumour)* – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
mercaptopurine	***Tablet:*** *50 mg.* ***Oral liquid:*** *20 mg/mL.* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Langerhans cell histiocytosis*
methotrexate	***Concentrated injection:*** *1000 mg/10 mL.* ***Injection:*** *50 mg/2 mL.* ***Powder for injection:*** *50 mg (as sodium) in vial.* ***Tablet:*** *2.5 mg (as sodium).* – *Acute lymphoblastic leukaemia* – *Acute promyelocytic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Langerhans cell histiocytosis* – *Osteosarcoma*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.* ***Powder for injection:*** *50 mg; 100 mg in vial.* – *Early stage colon cancer* – *Metastatic colorectal cancer*
paclitaxel	***Injection:*** *6 mg/mL in vial.* – *Ovarian germ cell tumour*
*pegaspargase** * *including quality-assured biosimilars*	***Injection:*** *3750 units/5 mL in vial.* ***Powder for injection:*** *3750 units in vial.* – *Acute lymphoblastic leukaemia*
procarbazine	***Capsule:*** *50 mg (as hydrochloride).* – *Hodgkin lymphoma*
realgar-Indigo naturalis formulation	***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).* – *Acute promyelocytic leukaemia*
tioguanine	***Solid oral dosage form:*** *40 mg.* – *Acute lymphoblastic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

vinblastine	***Injection:*** *10 mg/10 mL (sulfate) in vial.* ***Powder for injection:*** *10 mg (sulfate) in vial.* – *Anaplastic large cell lymphoma* – *Hodgkin lymphoma* – *Langerhans cell histiocytosis* – *Low-grade glioma* – *Ovarian germ cell tumour* – *Testicular germ cell tumour*
vincristine	***Injection:*** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.* ***Powder for injection:*** *1 mg; 5 mg (sulfate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Ewing sarcoma* – *Hodgkin lymphoma* – *Kaposi sarcoma* – *Langerhans cell histiocytosis* – *Low-grade glioma* – *Nephroblastoma (Wilms tumour)* – *Retinoblastoma* – *Rhabdomyosarcoma*
vinorelbine	***Capsule:*** *20 mg; 30 mg.* ***Injection:*** *10 mg/mL in 1 mL, 5 mL vial.* – *Rhabdomyosarcoma*

8.2.2 ***Targeted therapies***

Complementary List

all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* – *Acute promyelocytic leukaemia*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
everolimus	***Tablet:*** *2.5 mg; 5 mg; 7.5 mg; 10 mg.* ***Tablet (dispersible):*** *2 mg; 3 mg; 5 mg.* – *Subependymal giant cell astrocytoma*
imatinib	***Solid oral dosage form:*** *100 mg; 400 mg.* – *Chronic myeloid leukaemia* – *Gastrointestinal stromal tumour* – *Philadelphia chromosome positive acute lymphoblastic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

nilotinib	***Capsule:*** *150 mg; 200 mg.* – *Imatinib-resistant chronic myeloid leukaemia*
*rituximab** * *including quality-assured biosimilars*	***Injection (intravenous):*** *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma*

8.2.3 ***Immunomodulators***

Complementary List

*blinatumomab** * *including quality-assured biosimilars*	***Powder for concentrate for solution for infusion:*** *35 micrograms; 38.5 micrograms in vial.* – *B-cell acute lymphoblastic leukemia*
*filgrastim** * *including quality-assured biosimilars*	***Injection:*** *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.* ***Injection:*** *300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*
*pegfilgrastim** * *including quality-assured biosimilars*	***Injection:*** *6 mg/0.6 mL in pre-filled syringe.* – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy* – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy* – *To facilitate administration of dose dense chemotherapy regimens*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.4 *Hormones and antihormones*

Complementary List

dexamethasone	***Injection:*** *4 mg/mL dexamethasone phosphate (as sodium phosphate) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule.* ***Oral liquid:*** *2 mg/5 mL (as sodium phosphate).* ***Tablet:*** *2 mg; 4 mg (as dexamethasone base).* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma*
hydrocortisone	***Powder for injection:*** *100 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukaemia* – *Burkitt lymphoma*
methylprednisolone	***Powder for injection:*** *40 mg (as sodium succinate); 125 mg (as sodium succinate) in vial.* – *Acute lymphoblastic leukamia* – *Burkitt lymphoma*
☐ *prednisolone* *Therapeutic alternatives:* – *prednisone*	***Oral liquid:*** *5 mg/mL.* ***Tablet:*** *5 mg; 25 mg.* – *Acute lymphoblastic leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Diffuse large B-cell lymphoma* – *Hodgkin lymphoma* – *Langerhans cell histiocytosis*

8.2.5 *Supportive medicines*

Complementary List

allopurinol	***Powder for injection:*** *500 mg (as sodium).* ***Tablet:*** *100 mg; 300 mg.* – *Tumour lysis syndrome*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
mesna	***Injection*:*** *100 mg/mL in 4 mL, 10 mL ampoule.* ***Tablet:*** *400 mg; 600 mg.* * May also be used for oral administration. – *Burkitt lymphoma* – *Ewing sarcoma* – *Nephroblastoma (Wilms tumour)* – *Osteosarcoma* – *Ovarian germ cell tumours* – *Rhabdomyosarcoma* – *Testicular germ cell tumours*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg (with 1 mL solvent); 7.5 mg (with 5 mL solvent) in vial.* – *Tumour lysis syndrome*
9. THERAPEUTIC FOODS	
ready-to-use therapeutic food	**Biscuit or paste*** * of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.
10. MEDICINES AFFECTING THE BLOOD	
10.1 Antianaemia medicines	
ferrous salt	**Oral liquid:** equivalent to 9 mg/mL elemental iron; equivalent to 25 mg/mL elemental iron. **Tablet:** equivalent to 60 mg – 65 mg elemental iron.
folic acid	**Oral liquid:** 1 mg/mL. **Tablet:** 1 mg; 5 mg.
hydroxocobalamin	**Injection:** 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.
Complementary List	
☐ *erythropoiesis-stimulating agents** *Therapeutic alternatives:* – *epoetin alfa, beta and theta* – *darbepoetin alfa* * *including quality-assured biosimilars*	***Injection: pre-filled syringe*** *1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8 mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.*

10. MEDICINES AFFECTING THE BLOOD *(continued)*

10.2 Medicines affecting coagulation

desmopressin	**Injection:** 4 micrograms/mL (acetate) in 1 mL ampoule. **Nasal spray:** 150 micrograms (acetate) per actuation.
emicizumab	**Injection:** 12 mg/0.4 mL; 30 mg/mL; 60 mg/0.4 mL in vial.
☐ enoxaparin*	**Injection: ampoule or pre-filled syringe**
Therapeutic alternatives*: – dalteparin – nadroparin * including quality-assured biosimilars	20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
phytomenadione	**Injection:** 1 mg/0.5 mL;1 mg/mL; 10 mg/mL in ampoule. **Injection (mixed micelle solution):** 2 mg/0.2 mL; 10 mg/mL in ampoule. **Tablet:** 5 mg.
Complementary List	
heparin sodium	***Injection:** 1000 IU/mL; 5000 IU/mL in 1 mL ampoule or vial.*
protamine sulfate	***Injection:** 10 mg/mL in 5 mL ampoule or vial.*
☐ *warfarin* *Therapeutic alternatives:* – *acenocoumarol*	***Tablet:** 0.5 mg; 1 mg; 2 mg; 3 mg; 5 mg (sodium).*

10.3 Medicines for haemoglobinopathies

10.3.1 ***Medicines for sickle-cell disease***

☐ deferasirox	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg.
Therapeutic alternatives: – deferiprone	**Tablet (film-coated):** 90 mg; 180 mg; 360 mg.
hydroxyurea (hydroxycarbamide)	**Solid oral dosage form:** 100 mg; 200 mg; 500 mg; 1 g.
Complementary List	
deferoxamine	***Powder for injection:** 500 mg (mesilate) in vial.*

10. MEDICINES AFFECTING THE BLOOD *(continued)*

10.3.2 *Medicines for thalassaemias*

☐ deferasirox	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg.
Therapeutic alternatives:	
– deferiprone	**Tablet (film-coated):** 90 mg; 180 mg; 360 mg.

Complementary List

deferoxamine	***Powder for injection:*** *500 mg (mesilate) in vial.*

11. BLOOD PRODUCTS, COAGULATION FACTORS, AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population.

All blood and plasma-derived products should comply with the WHO requirements.

☐ cryoprecipitate, pathogen-reduced	**Injection:** frozen liquid in bag or lyophilized powder in vial containing:
Therapeutic alternatives:	– > 50 IU Factor VIII
– cryoprecipitate, native*	– > 100 IU vWF
* native cryoprecipitate should only be used in situations of life-threatening haemorrhage when pathogen-reduced cryoprecipitate is not available.	– > 140 mg clottable fibrinogen per unit
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	

11.2 Human immunoglobulins

anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.

11. BLOOD PRODUCTS, COAGULATION FACTORS, AND PLASMA SUBSTITUTES *(continued)*

Complementary List

normal immunoglobulin	***Intramuscular administration:*** *16% protein solution.* ***Subcutaneous administration:*** *15%; 16% protein solution.* – *Primary immune deficiency* ***Intravenous administration:*** *5%; 10% protein solution.* – *Primary immune deficiency* – *Kawasaki disease* – *Langerhans cell histiocytosis*

11.3 *Coagulation factors*

coagulation factor VIII, plasma-derived	**Powder for injection:** 250 IU; 500 IU; 1000 IU in vial.
coagulation factor IX, plasma-derived	**Powder for injection:** 500 IU; 1000 IU in vial.
coagulation factor VIII, recombinant	**Lyophilized powder for solution for injection:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU in vial.
coagulation factor IX, recombinant	**Lyophilized powder for solution for injection:** 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU, 4000 IU in vial.

11.4 Plasma substitutes

☐ dextran 70 Therapeutic alternatives: – Polygeline injectable solution 3.5%	**Injectable solution:** 6%.

12. CARDIOVASCULAR MEDICINES

~~12.1 Antianginal medicines~~

~~12.2 Antiarrhythmic medicines~~

12.3 Antihypertensive medicines

☐ enalapril Therapeutic alternatives: – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)	**Oral liquid:** 1 mg/mL (as hydrogen maleate). **Tablet:** 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).

12. CARDIOVASCULAR MEDICINES *(continued)*

12.4 Medicines used in heart failure

furosemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule. **Oral liquid:** 20 mg/5 mL; 50 mg/5 mL. **Tablet:** 20 mg; 40 mg.
Complementary List	
digoxin	***Injection:*** *100 micrograms/mL in 1 mL ampoule; 250 micrograms/mL in 2 mL ampoule.* ***Oral liquid:*** *50 micrograms/mL.* ***Tablet:*** *62.5 micrograms; 125 micrograms; 250 micrograms.*
dopamine	***Injection:*** *40 mg/mL (hydrochloride) in 5 mL vial.*

~~12.5 Antithrombotic medicines~~

~~12.6 Lipid-lowering agents~~

~~12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease~~

13. DERMATOLOGICAL MEDICINES

13.1 Antifungal medicines

☐ miconazole Therapeutic alternatives: – 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
terbinafine	**Cream or ointment:** 1% (hydrochloride).

13.2 Anti-infective medicines

mupirocin	**Cream:** 2% (as calcium). **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] > 2 months.

13. DERMATOLOGICAL MEDICINES *(continued)*

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a] Therapeutic alternatives: – 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))	**Cream or ointment:** 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine	**Lotion.**
hydrocortisone	**Cream or ointment:** 1% (acetate).

13.4 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	**Cream or lotion:** 5%.
☐ calcipotriol Therapeutic alternatives: – calcitriol – tacalcitol	**Cream or ointment:** 50 micrograms/mL (0.005%). **Lotion:** 50 micrograms/mL (0.005%).
coal tar	**Solution:** 5%.
☐ podophyllum resin Therapeutic alternatives: – podophyllotoxin	**Solution:** 10% to 25%.
salicylic acid	**Solution:** 5%.
urea	**Cream or ointment:** 5%; 10%.

Complementary List

☐ *adalimumab** *Therapeutic alternatives:* – *certolizumab pegol* – *etanercept* – *infliximab* * including quality-assured biosimilars	***Injection:*** *10 mg/0.2 mL; 20 mg/0.2 mL; 20 mg/0 4 mL; 40 mg/0.4 mL; 40 mg/0.8 mL; 80 mg/0.8 mL in pre-filled syringe or pre-filled pen.*
methotrexate	***Tablet:*** *2.5 mg; 10 mg (as sodium).*
*ustekinumab** ** including quality-assured biosimilars*	***Injection:*** *45 mg/0.5 mL in vial or pre-filled syringe; 90 mg/mL in pre-filled syringe.*

13. DERMATOLOGICAL MEDICINES *(continued)*

13.5 Scabicides and pediculicides

☐ benzyl benzoate [a] Therapeutic alternatives: – precipitated sulfur topical ointment	**Lotion:** 25%. [a] > 2 years.
permethrin	**Cream:** 5%. **Lotion:** 1%.

13.6 Moisturizers

urea	**Cream:** 5%
glycerol	**Cream:** 15% to 20%.

13.7 Sunscreens

sunscreen, broad-spectrum	**Topical:** Therapeutic broad-spectrum sunscreens should contain proven active ingredients in appropriate amounts to absorb or filter UVA and UVB radiation, and have a high sun protection factor (SPF).

14. DIAGNOSTIC AGENTS

14.1 Ophthalmic medicines

fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide Therapeutic alternatives: – atropine – cyclopentolate	**Eye drops:** 0.5%.

14.2 Radiocontrast media

Complementary List

barium sulfate	***Aqueous suspension.***

15. ANTISEPTICS AND DISINFECTANTS

15.1 Antiseptics

☐ chlorhexidine Therapeutic alternatives to be reviewed	**Solution:** 5% (digluconate).

15. ANTISEPTICS AND DISINFECTANTS *(continued)*	
☐ ethanol Therapeutic alternatives: – propanol	**Solution:** 70% (denatured).
☐ povidone iodine Therapeutic alternatives: – iodine	**Solution:** 10% (equivalent to 1% available iodine).
15.2 Disinfectants	
alcohol based hand rub	**Solution:** containing ethanol 80% volume/volume. **Solution:** containing isopropyl alcohol 75% volume/volume.
chlorine base compound	**Liquid:** (0.1% available chlorine) for solution. **Powder:** (0.1% available chlorine) for solution. **Solid:** (0.1% available chlorine) for solution.
☐ chloroxylenol Therapeutic alternatives: – 4th level ATC chemical subgroup (D08AE Phenol and derivatives)	**Solution:** 4.8%.
glutaral	**Solution:** 2%.
hypochlorous acid	**Solution (aqueous):** containing hypochlorous acid ≥ 150 parts per million.
16. DIURETICS	
furosemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule. **Oral liquid:** 20 mg/5 mL; 50 mg/5 mL. **Tablet:** 20 mg; 40 mg.
Complementary List	
☐ *hydrochlorothiazide* *Therapeutic alternatives:* – *chlorothiazide* – *chlortalidone*	***Solid oral dosage form:*** *12.5 mg; 25 mg.*
mannitol	***Solution for infusion:*** *10%; 20%.*
spironolactone	***Oral liquid:*** *25 mg/5 mL.* ***Tablet:*** *12.5 mg; 25 mg.*

17. GASTROINTESTINAL MEDICINES

Complementary List

pancreatic enzymes	*C**apsule (modified release)**:** 10 000 lipase units + 8000 amylase units + 600 protease units; 25 000 lipase units + 18 000 amylase units + 1000 protease units.*
	** Units expressed in Ph.Eur*

17.1 Antiulcer medicines

☐ omeprazole Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	**Powder for oral liquid:** 1 mg/mL; 4 mg/mL. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BA H_2-receptor antagonists) excluding combinations	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL dexamethasone phosphate (as sodium phosphate salt) (equivalent to 3.3 mg/mL dexamethasone base) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL (as sodium phosphate). **Tablet:** 0.5 mg; 0.75 mg; 1.5 mg; 2 mg; 4 mg (as dexamethasone base).
metoclopramide	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL. **Tablet (scored):** 10 mg (hydrochloride).
☐ ondansetron Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg/mL in 2 mL, 4 mL ampoule (as hydrochloride dihydrate). **Oral liquid:** 4 mg/5 mL (as hydrochloride dihydrate). **Solid oral dosage form:** 4 mg; 8 mg (as hydrochloride dihydrate).

Complementary list

aprepitant	***Powder for oral suspension:** 125 mg in sachet.*

17. GASTROINTESTINAL MEDICINES *(continued)*

~~**17.3 Anti-inflammatory medicines**~~

~~**17.4 Laxatives**~~

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate	**Co-package containing:** **ORS powder for dilution** (see Section 17.5.1) – zinc sulfate **tablet (dispersible, scored):** 20 mg (see Section 17.5.2)

17.5.1 *Oral rehydration*

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mEq or mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17.5.2 *Medicines for diarrhoea*

zinc sulfate*

Tablet (dispersible, scored): 20 mg.

* In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone

Oral liquid: 100 micrograms/mL (acetate).

Tablet: 100 micrograms (acetate).

hydrocortisone

Granules: 0.5 mg; 1 mg; 2 mg; 5 mg in capsule.

Tablet: 5 mg; 10 mg; 20 mg.

☐ prednisolone

Tablet: 1 mg.

Therapeutic alternatives:

– prednisone

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

~~**18.2 Androgens**~~

~~**18.3 Estrogens**~~

~~**18.4 Progestogens**~~

18.5 Medicines for diabetes

18.5.1 ***Insulins***

☐ insulin (analogue, long-acting)* Therapeutic alternatives: – insulin glargine – insulin degludec – insulin detemir * *including quality-assured biosimilars*	**Injection solution:** 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
☐ insulin (analogue, rapid-acting)* Therapeutic alternatives: – insulin lispro – insulin aspart – insulin glulisine * *including quality-assured biosimilars*	**Injection solution:** 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
insulin (human, intermediate-acting)* * *including quality-assured biosimilars*	**Injection suspension:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).
insulin (human, short-acting)* * *including quality-assured biosimilars*	**Injection solution:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.

18.5.2 ***Oral hypoglycaemic agents***

Complementary List

metformin	***Tablet:*** *500 mg (hydrochloride).*

18.6 Medicines for hypoglycaemia

glucagon	**Injection:** 1 mg/mL.

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

Complementary List

diazoxide	***Oral liquid:*** *50 mg/mL.* ***Tablet:*** *50 mg.*

18.7 Thyroid hormones and antithyroid medicines

levothyroxine	**Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).

Complementary List

iodine + potassium iodide (Lugol's solution)	***Oral liquid (aqueous):*** *5% w/v + 10% w/v.*
☐ *methimazole* *Therapeutic alternatives:* *carbimazole (depending on local availability)*	***Tablet:*** *5 mg; 10 mg.*
potassium iodide	***Tablet (scored):*** *65 mg.*
*propylthiouracil**	***Tablet:*** *50 mg.* * *For use when alternative first-line treatment is not appropriate or available*

~~18.8 Medicines for disorders of the pituitary hormone system~~

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD)	**Injection**.

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus monoclonal antibodies* * *including quality-assured biosimilars*	**Injection:** 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human). **Injection:** 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).
antivenom immunoglobulin*	**Injection.** *Exact type to be defined locally.

19. IMMUNOLOGICALS *(continued)*	
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	**Injection:** 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial.

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts (SAGE) on Immunization.

WHO vaccine position papers are periodically revised to assess the need for an update. The list below details the vaccines for which there is a recommendation from WHO and a corresponding WHO vaccine position paper as at May 2025. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Vaccines included on the Model Lists reflect the recommendations of SAGE, as per the available policy reflected in the WHO vaccine position papers.

Countries are encouraged to consider inclusion of specific vaccines into their national immunization schedule based on national priorities by carefully assessing various criteria such as local burden of disease and disease epidemiology, acceptability, cost, cost-effectiveness, programmatic feasibility, regulatory status, and availability of products.

All vaccines should comply with the WHO requirements for biological substances.

BCG vaccine

cholera vaccine

dengue vaccine

diphtheria vaccine

Ebola vaccine

Haemophilus influenzae type b vaccine

hepatitis A vaccine

hepatitis B vaccine

19. IMMUNOLOGICALS *(continued)*	
human papilloma virus (HPV) vaccine	
influenza vaccine (seasonal)	
Japanese encephalitis vaccine	
malaria vaccine	
measles vaccine	
meningococcal meningitis vaccine	
mpox vaccine	
mumps vaccine	
pertussis vaccine	
pneumococcal vaccine	
poliomyelitis vaccine	
rabies vaccine	
rotavirus vaccine	
rubella vaccine	
tetanus vaccine	
tick-borne encephalitis vaccine	
typhoid vaccine	
varicella vaccine	
yellow fever vaccine	

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS	
neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule.
☐ vecuronium Therapeutic alternatives: – atracurium	**Powder for injection:** 10 mg (bromide) in vial.

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS *(continued)*

Complementary List

pyridostigmine	***Injection:*** *5 mg/mL (bromide) in ampoule or vial.* ***Tablet (scored):*** *60 mg (bromide).*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – Trachoma
erythromycin	**Ointment:** 0.5%. – Infections due to Chlamydia trachomatis or Neisseria gonorrhoeae
☐ gentamicin Therapeutic alternatives: – amikacin – kanamycin – netilmicin – tobramycin	**Solution (eye drops):** 0.3% (sulfate). – Bacterial blepharitis – Bacterial conjunctivitis
natamycin	**Suspension (eye drops):** 5%. – Fungal keratitis
☐ ofloxacin Therapeutic alternatives: – 4th level ATC chemical subgroup (S01AE Fluoroquinolones)	**Solution (eye drops):** 0.3%. – Bacterial conjunctivitis – Bacterial keratitis
☐ tetracycline Therapeutic alternatives: – chlortetracycline – oxytetracycline	**Eye ointment:** 1% (hydrochloride). – Bacterial blepharitis – Bacterial conjunctivitis – Bacterial keratitis – Trachoma

21.2 Anti-inflammatory agents

☐ prednisolone Therapeutic alternatives to be reviewed	**Solution (eye drops):** 0.5% (sodium phosphate).

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

21.3 Local anaesthetics

☐ tetracaine [a]	**Solution (eye drops):** 0.5% (hydrochloride).
Therapeutic alternatives: – 4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations	[a] Not in preterm neonates.

~~21.4 Miotics and antiglaucoma medicines~~

21.5 Mydriatics

☐ atropine [a]	**Solution** (eye drops): 0.1%; 0.5%; 1% (sulfate).
Therapeutic alternatives: – cyclopentolate hydrochloride – homatropine hydrobromide	[a] > 3 months.
Complementary List	
epinephrine (adrenaline)	***Solution (eye drops):** 2% (as hydrochloride).*

~~21.6 Anti-vascular endothelial growth factor (VEGF) preparations~~

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

~~22.1 Contraceptives~~

~~22.2 Ovulation inducers~~

~~22.3 Uterotonics~~

~~22.4 Medicines for medical abortion~~

~~22.5 Antioxytocics (tocolytics)~~

~~22.6 Other medicines administered to the mother~~

22.7 Medicines administered to the neonate

caffeine citrate	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL). **Oral liquid:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

Complementary List

☐ *alprostadil (prostaglandin E1)* *Therapeutic alternatives:* – *dinoprostone (prostaglandin E2)*	***Solution for injection:*** *0.5 mg/mL in alcohol.*
beractant	***Suspension for intratracheal instillation:*** *25 mg/mL.*
☐ *ibuprofen* *Therapeutic alternatives:* – *indometacin*	***Solution for injection:*** *5 mg/mL.*
poractant alfa	***Suspension for intratracheal instillation:*** *80 mg/mL.*

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution	***Solution:*** *of appropriate composition in accordance with local clinical guidelines.*

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

~~**24.1 Medicines used in psychotic disorders**~~

~~**24.2 Medicines used in mood disorders**~~

~~***24.2.1 Medicines used in depressive disorders***~~

~~***24.2.2 Medicines used in bipolar disorders***~~

~~**24.3 Medicines for anxiety disorders**~~

~~**24.4 Medicines used for obsessive compulsive disorders**~~

~~**24.5 Medicines for disorders due to psychoactive substance use**~~

~~***24.5.1 Medicines for alcohol use disorders***~~

~~***24.5.2 Medicines for nicotine use disorders***~~

~~***24.5.3 Medicines for opioid use disorders***~~

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines

☐ budesonide Therapeutic alternatives: – beclometasone – ciclesonide – fluticasone – mometasone	**Powder for inhalation:** 100 micrograms per actuation; 200 micrograms per actuation in dry powder inhaler. **Suspension for inhalation:** 100 micrograms per actuation; 200 micrograms per actuation in pressurized metered-dose inhaler.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
☐ salbutamol Therapeutic alternatives: – terbutaline	**Injection:** 500 micrograms/mL (as sulfate) in 1 mL, 5 mL ampoule. **Solution for inhalation:** 100 micrograms (as sulfate) per actuation in pressurized metered-dose inhaler; 2.5 mg/2.5 mL, 5 mg/2.5 mL (as sulfate) in 2.5 mL single-dose ampoules for use in nebulizers; 5 mg/mL (as sulfate) in multi-dose bottle for use in nebulizers.

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na^+ 150 mmol/L and Cl^- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na^+ 75 mmol/L and Cl^- 75 mmol/L).
potassium chloride	**Solution for dilution:** 7.5% (equivalent to K^+ 1 mmol/mL and Cl^- 1 mmol/mL); 15% (equivalent to K^+ 2 mmol/mL and Cl^- 2 mmol/mL).
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na^+ 154 mmol/L, Cl^- 154 mmol/L).

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES *(continued)*	
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na^+ 167 mmol/L, HCO_3^- 167 mmol/L). **Solution:** 8.4% in 10 mL ampoule (equivalent to Na^+ 1000 mmol/L, HCO_3^- 1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**
26.3 Miscellaneous	
water for injection	2 mL; 5 mL; 10 mL ampoules.
27. VITAMINS AND MINERALS	
ascorbic acid	**Tablet:** 50 mg.
☐ colecalciferol Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
iodine	**Iodized oil:** 480 mg iodine/mL in 10 mL ampoule or vial (oral or injectable).
multiple micronutrient powder	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values
pyridoxine	**Tablet:** 10 mg; 25 mg (hydrochloride).
retinol	**Soft capsule:** 100 000 IU; 200 000 IU (as acetate or palmitate). **Oral liquid:** 100 000 IU/mL (as palmitate). **Water-miscible injection:** 50 000 IU/mL (as palmitate) in 2 mL ampoule or vial.
riboflavin	**Tablet:** 5 mg.
thiamine	**Injection:** 50 mg/mL (hydrochloride) in ampoule or vial. **Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	***Injection:** 100 mg/mL in 10 mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES

acetic acid	**Solution (ear drops):** 2%.
☐ budesonide Therapeutic alternatives to be reviewed	**Nasal spray:** 32 micrograms; 64 micrograms per actuation.
☐ ciprofloxacin Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline Therapeutic alternatives to be reviewed	**Nasal drops:** 0.05%. **Nasal spray:** 0.05%.

29. MEDICINES FOR DISEASES OF JOINTS

~~**29.1 Medicines used to treat gout**~~

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

Complementary List

hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium).*

29.3 Medicines for juvenile joint diseases

Complementary List

*acetylsalicylic acid**	***Suppository:*** *150 mg; 300 mg.* ***Tablet:*** *75 mg to 500 mg.* ***Tablet (dispersible):*** *75 mg; 300 mg; 500 mg.* * *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*
☐ *adalimumab** *Therapeutic alternatives*:* – *etanercept* – *infliximab* * *including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL; 20 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.4 mL; 40 mg/0.8 mL in pre-filled syringe or pre-filled pen.*
methotrexate	***Tablet:*** *2.5 mg (as sodium).*
☐ *triamcinolone hexacetonide* *Therapeutic alternatives:* – *triamcinolone acetonide*	***Injection:*** *20 mg/mL in vial.*

30. DENTAL MEDICINES AND PREPARATIONS	
fluoride	**Gel:** containing 2500 to 12 500 ppm fluoride (any type). **Mouthrinse:** containing 230 to 900 ppm fluoride (any type). **Toothpaste, cream or gel:** containing 1000 to 1500 ppm fluoride (any type). **Varnish:** containing 22 500 ppm fluoride (any type).
glass ionomer cement	**Single-use capsules:** 0.4 g powder + 0.09 mL liquid. **Multi-use bottle:** powder + liquid. Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
resin-based composite (low-viscosity)*	**Single-use applicator or multi-use bottle.** * of any type for use as dental sealant.
resin-based composite (high-viscosity)*	**Single-use capsule or multi-use syringe.** * of any type for use as dental filling material.
silver diamine fluoride	**Solution:** 38% w/v.

Annex 3

Alphabetical list of essential medicines (with ATC codes & section numbers)

Medicine or item as in EML/EMLc	ATC code	Section
abacavir	J05AF06	6.4.2.1
abacavir + dolutegravir + lamivudine	J05AR13	6.4.2.5
abacavir + lamivudine	J05AR02	6.4.2.5
abiraterone	L02BX03	8.2.4
acamprosate	N07BB03	24.5.1
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5.1
acetylsalicylic acid	N02BA01	2.1; 5.1.5.1; 29.3
acetylsalicylic acid + atorvastatin + ramipril	C10BX06	12.7
acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide	–	12.7
aciclovir	J05AB01	5.1.6.2; 6.4.1
aciclovir	S01AD03	21.1
adalimumab	L04AB04	8.1
albendazole	P02CA03	6.1.1; 6.1.2; 6.1.4
alcohol based hand rub	D08AX08	15.2
allopurinol	M04AA01	8.2.5; 29.1
all-trans retinoid acid (ATRA)	L01XF01	8.2.2
alteplase	B01AD02	12.5.2
amidotriozate	V08AA01	14.2
amikacin	J01GB06	6.2.1; 6.2.5
amiloride	C03DB01	16
amiodarone	C01BD01	12.2

Medicine or item as in EML	ATC code	Section
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amodiaquine – sulfadoxine + pyrimethamine	P01BA06 P01BD51	6.5.3.2
amoxicillin	J01CA04	5.1.6.1; 6.2.1
amoxicillin + clavulanic acid	J01CR02	6.2.1; 6.2.5
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	5.1.6.1; 6.2.1
anastrozole	L02BG03	8.2.4
ansuvimab	J06BD04	6.7
anti-D immunoglobulin	J06BB01	11.2.1
anti-rabies immunoglobulin	J06BB05	11.2.1
anti-rabies virus monoclonal antibodies	–	19.2
anti-tetanus immunoglobulin	J06BB02	11.2.1
antivenom immunoglobulin	–	19.2
aprepitant	A04AD12	17.2
arpraziquantel	P02BA03	6.1.3
arsenic trioxide	L01XX27	8.2.1
artemether	P01BE02	6.5.3.1
artemether + lumefantrine	P01BF01	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate + amodiaquine	P01BF03	6.5.3.1
artesunate + mefloquine	P01BF02	6.5.3.1
artesunate + pyronaridine tetraphosphate	P01BF06	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2.1
atazanavir + ritonavir	J05AR23	6.4.2.3
atoltivimab + maftivimab + odesivimab	–	6.7
atorvastatin + perindopril + amlodipine	C10BX11	12.7
atracurium	M03AC04	20

Medicine or item as in EML	ATC code	Section
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 29.2
azithromycin	J01FA10	6.2.2
azithromycin	S01AA26	21.1
baclofen	M03BX01	5.1.4
barium sulfate	V08BA01	14.2
BCG vaccine	L03AX03	19.3
bedaquiline	J04AK05	6.2.5
bendamustine	L01AA09	8.2.1
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.4
benzyl benzoate	P03AX01	13.5
benzylpenicillin	J01CE01	5.1.6.1; 6.2.1
beractant	R07AA	22.7
betamethasone	D07AC01	13.3
bevacizumab	S01LA08	21.6
bicalutamide	L02BB03	8.2.4
biperiden	N04AA02	5.1.3
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2.1
blinatumomab	L01FX07	8.2.3
bortezomib	L01XG01	8.2.2
budesonide	R03BA02	25.1
budesonide	R01AD05	28
budesonide + formoterol	R03AK07	25.1
bupivacaine	N01BB01	1.2
bupropion	N06AX12	24.5.2
cabergoline	G02CB03	18.8

Medicine or item as in EML	ATC code	Section
caffeine citrate	R07AB	22.7
calamine	D02AB	13.3
calcipotriol	D05AX02	13.4
calcium	A12AA20	27
calcium folinate	V03AF03	8.2.1
calcium gluconate	A12AA03	4.2; 27
capecitabine	L01BC06	8.2.1
carbamazepine	N03AF01	5.1.1; 24.2.2
carbetocin	H01BB03	22.3
carboplatin	L01XA02	8.2.1
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1
cefiderocol	J01DI04	6.2.3
cefixime	J01DD08	6.2.2
cefotaxime	J01DD01	5.1.6.1; 6.2.2
ceftazidime	J01DD02	6.2.2
ceftazidime + avibactam	J01DD52	6.2.3
ceftolozane + tazobactam	J01DI54	6.2.3
ceftriaxone	J01DD04	5.1.6.1; 6.2.2
cefuroxime	J01DC02	6.2.2
charcoal, activated	A07BA01	4.1
chlorambucil	L01AA02	8.2.1
chloramphenicol	J01BA01	5.1.6.1; 6.2.1
chlorhexidine	D08AC02	15.1; 22.7
chlorine base compound	–	15.2
chloroquine	P01BA01	6.5.3.1; 6.5.3.2; 6.5.3.3; 29.2
chloroxylenol	D08AE05	15.2
cholera vaccine	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
cisplatin	L01XA01	8.2.1

Medicine or item as in EML	ATC code	Section
cladribine	L04AA40	5.1.2
clarithromycin	J01FA09	6.2.2
clindamycin	J01FF01	6.2.1
clofazimine	J04BA01	6.2.4; 6.2.5
clomifene	G03GB02	22.2
clomipramine	N06AA04	24.4
clopidogrel	B01AC04	12.5.1
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
clozapine	N05AH02	24.1
coagulation factor VIII	B02BD02	11.3
coagulation factor VIII (recombinant)	B02BD02	11.3
coagulation factor IX	B02BD04	11.3
coagulation factor IX (recombinant)	B02BD04	11.3
coal tar	D05AA	13.4
codeine	R05DA04	2.2
colecalciferol	A11CC05	27
colistin	J01XB01	6.2.3
condoms	–	22.1.4
copper-containing device	G02BA02	22.1.3
cryoprecipitate, pathogen-reduced	B05AA02	11.1
cyclizine	R06AE03	2.3
cyclophosphamide	L01AA01	8.2.1
cycloserine	J04AB01	6.2.5
cytarabine	L01BC01	8.2.1
cytisine	N07BA04	24.5.2
dabigatran	B01AE07	10.2
dacarbazine	L01AX04	8.2.1
daclatasvir	J05AP07	6.4.4.2.1
daclatasvir + sofosbuvir	J05AP07 J05AP08	6.4.4.2.1

Medicine or item as in EML	ATC code	Section
dactinomycin	L01DA01	8.2.1
dapsone	J04BA02	6.2.4
darbepoetin alfa	B03XA02	10.1
darunavir	J05AE10	6.4.2.3
dasatinib	L01EA02	8.2.2
daunorubicin	L01DB02	8.2.1
deferasirox	V03AC03	10.3
deferoxamine	V03AC01	4.2; 10.3
delamanid	J04AK06	6.2.5
dengue vaccine	J07BX04	19.3
desmopressin	H01BA02	10.2
dexamethasone	H02AB02	2.3; 3; 8.2.4; 17.2; 22.6
dextran 70	B05AA05	11.4
diaphrams	–	22.1.4
diazepam	N05BA01	2.3; 5.1.1; 24.3
diazoxide	V03AH01	18.6
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
dihydroartemisinin + piperaquine phopshate	P01BF05	6.5.3.1
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria vaccine	J07AF01	19.3
docetaxel	L01CD02	8.2.1
docusate sodium	A06AA02	2.3
dolutegravir	J05AJ03	6.4.2.4
dolutegravir + lamivudine + tenofovir	J05AR27	6.4.2.5
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2.1
doxycycline	J01AA02	6.2.1; 6.5.3.1; 6.5.3.2

Medicine or item as in EML	ATC code	Section
Ebola vaccine	J07BX02	19.3
efavirenz	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir disoproxil	J05AR06	6.4.2.5
efavirenz + lamivudine + tenofovir disoproxil	J05AR11	6.4.2.5
eflornithine	P01CX03	6.5.5.1
elexacaftor + tezacaftor + ivacaftor	R07AX32	7
emicizumab	B02BX06	10.2
empagliflozin	A10BK03	18.5.2
emtricitabine + tenofovir disoproxil	J05AR03	6.4.2.5
enalapril	C09AA02	12.3; 12.4
enoxaparin	B01AB05	10.2
entecavir	J05AF10	6.4.4.1.1
ephedrine	C01CA26	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
equine rabies immunoglobulin	J06BB05	19.2
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.3
erlotinib	L01EB02	8.2.2
erythromycin	S01AA17	21.1
erythropoiesis-stimulating agents	B03XA01 B03XA02 B03XA03	10.1
estradiol cypionate + medroxyprogesterone acetate	G03AA17	22.1.2
ethambutol	J04AK02	6.2.5
ethambutol + isoniazid + pyrazinamide + rifampicin	J04AM06	6.2.5
ethambutol + isoniazid + rifampicin	J04AM07	6.2.5
ethanol	D08AX08	15.1
ethinylestradiol + etonogestrel	G02BB01	22.1.6

Medicine or item as in EML	ATC code	Section
ethinylestradiol + levonorgestrel	G03AA07	22.1.1
ethinylestradiol + norethisterone	G03AA05	22.1.1
ethionamide	J04AD03	6.2.5
ethosuximide	N03AD01	5.1
etonogestrel-releasing implant	G03AC08	22.1.5
etoposide	L01CB01	8.2.1
everolimus	L01EG02	8.2.2
fentanyl	N02AB03	2.2
ferrous salt	B03AA02 B03AA07	10.1
ferrous salt + folic acid	B03AD02 B03AD03	10.1
fexinidazole	P01CA03	6.5.5.1
filgrastim	L03AA02	8.2.3
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludarabine	L01BB05	8.2.1
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluoride	A01AA	30
fluorouracil	L01BC02	8.2.1; 13.4
fluoxetine	N06AB03	2.3; 24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2
fosfomycin	J01XX01	6.2.3
fresh frozen plasma	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gemcitabine	L01BC05	8.2.1
gentamicin	J01GB03	5.1.6.1; 6.2.1

Medicine or item as in EML	ATC code	Section
gentamicin	S01AA11	21.1
glass ionomer cement	–	30
glatiramer acetate	L03AX13	5.1.2
glecaprevir + pibrentasvir	J05AP57	6.4.4.2.1
gliclazide	A10BB09	18.5.2
glucagon	H04AA01	18.6
glucose	B05CX01	26.2
glucose with sodium chloride	B05BA03	26.2
glutaral	–	15.2
glycerol	D02AX D02AC	13.6
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
Haemophilus influenzae type b vaccine	J07AG01	19.3
haloperidol	N05AD01	2.3; 24.1
heparin sodium	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hepatitis E vaccine	J07BC	19.3
human papilloma virus (HPV) vaccine	J07BM	19.3
hydralazine	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.2.4; 18.1
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2.1; 10.3
hydroxychloroquine	P01BA02	29.2
hyoscine butylbromide	A03BB01	2.3
hyoscine hydrobromide	A04AD01	2.3

Medicine or item as in EML	ATC code	Section
ibrutinib	L01EL01	8.2.2
ibuprofen	C01EB16	22.7
ibuprofen	M01AE01	2.1; 7.1; 5.1.5.1
ifosfamide	L01AA06	8.2.1
imatinib	L01EA01	8.2.2
influenza vaccine	J07BB	19.3
insulin (analogue, long-acting)	A10AE	18.5.1
insulin (analogue, rapid-acting)	A10AB	18.5.1
insulin (human, intermediate-acting)	A10AC01	18.5.1
insulin (human, short-acting)	A10AB01	18.5.1
intraperitoneal dialysis solution	–	23
iodine	H03CA	27
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
irinotecan	L01CE02	8.2.1
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.5
isoniazid + pyrazinamide + rifampicin	J04AM05	6.2.5
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	J04AM08	6.4.2.6
isoniazid + rifampicin	J04AM02	6.2.5
isoniazid + rifapentine	J04AC51	6.2.5
isosorbide dinitrate	C01DA08	12.1
itraconazole	J02AC02	6.3
ivacaftor	R07AX02	7
ivermectin	P02CF01	6.1.1; 6.1.2; 6.6
Japanese encephalitis vaccine	J07BA02 J07BA03	19.3
ketamine	N01AX03	1.1.2

Medicine or item as in EML	ATC code	Section
lactulose	A06AD11	2.3
lamivudine	J05AF05	6.4.2.1
lamivudine + zidovudine	J05AR01	6.4.2.5
lamotrigine	N03AX09	5.1.1
latanoprost	S01EE01	21.4
ledipasvir + sofosbuvir	J05AP51	6.4.4.2.2
lenalidomide	L04AX04	8.2.3
letrozole	L02BG04	22.2
leuprorelin	L02AE02	8.2.4
levamisole	P02CE01	6.1.1
levetiracetam	N03AX14	5.1.1
levodopa + carbidopa	N04BA02	5.1.3
levofloxacin	J01MA12	6.2.5
levonorgestrel	G03AC03	22.2.1
levonorgestrel	G03AD01	22.2.1
levonorgestrel-releasing implant	G03AC03	22.1.5
levonorgestrel-releasing intrauterine system	G02BA03	22.1.3
levothyroxine	H03AA01	18.7
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine + epinephrine	N01BB52	1.2
linezolid	J01XX08	6.2.3; 6.2.5
lisinopril + amlodipine	C09BB03	12.3
lisinopril + hydrochlorothiazide	C09BA03	12.3
lithium carbonate	N05AN01	24.2.2
long-acting insulin analogues	A10AE04 A10AE05 A10AE06	18.5.1
loperamide	A07DA03	2.3
lopinavir + ritonavir	J05AR10	6.4.2.3
loratadine	R06AX13	3

Medicine or item as in EML	ATC code	Section
lorazepam	N05BA06	5.1.1
losartan	C09CA01	12.3; 12.4
Lugol's solution	H03CA	18.7
magnesium sulfate	B05XA05	5.1.1
malaria vaccine	J07XA01	19.3
mannitol	B05BC01	16
measles vaccine	J07BD01	19.3
mebendazole	P02CA01	6.1.1; 6.1.4
medroxyprogesterone acetate	G03AC06	22.1.2
medroxyprogesterone acetate	G03DA02	18.4
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
melphalan	L01AA03	8.2.1
meningococcal meningitis vaccine	J07AH	19.3
mercaptopurine	L01BB02	8.2.1
meropenem	J01DH02	5.1.6.1; 6.2.2; 6.2.5
meropenem + vaborbactam	J01DH52	6.2.3
mesna	V03AF01	8.2.5
metformin	A10BA02	18.5.2
methadone	N07BC02	2.2; 24.5
methimazole	H03BB02	18.7
methotrexate	L01BA01	8.2.1
methotrexate	L04AX03	29.2
methyldopa	C02AB01	12.3
methylprednisolone	H02AB04	8.2.4
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metronidazole	J01XD01	6.2.1

Medicine or item as in EML	ATC code	Section
metronidazole	P01AB01	6.5.1
micafungin	J02AX05	6.3
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3; 2.3; 5.1.1
mifepristone – misoprostol	G03XB51	22.4
miltefosine	P01CX04	6.5.2
misoprostol	G02AD06	22.4
morphine	N02AA01	1.3; 2.2
moxifloxacin	J01MA14	6.2.5
mpox vaccine	J07BX01	19.3
multiple micronutrient powder	A11AA01	27
multiple micronutrient supplement	A11AA01	22.6
mumps vaccine	J07BE01	19.3
mupirocin	D06AX09	13.2
naloxone	V03AB15	4.2
naltrexone	N07BB04	24.5.1
natamycin	S01AA10	21.1
neostigmine	N07AA01	5.2.2; 20
nevirapine	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nicotine replacement therapy	N07BA01	24.5
nifedipine	C08CA05	22.5
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nilotinib	L01EA03	8.2.2
nitrofurantoin	J01XE01	6.2.1
nitrous oxide	N01AX13	1.1.1
nivolumab	L01FF01	8.2.3
norethisterone enantate	G03AC01	22.1.2
normal immunoglobulin	J06BA	5.2.1; 11.2.1
nystatin	A07AA02	6.3

Medicine or item as in EML	ATC code	Section
nystatin	G01AA01	6.3
octreotide	H01CB02	18.8
ofloxacin	S01AE01	21.1
olanzapine	N05AH03	24.1
omeprazole	A02BC01	17.1
ondansetron	A04AA01	2.3; 17.2
oral rehydration salts	A07CA	17.5.1; 26.1
oral rehydration salts – zinc sulfate	A07CA A12CB01	17.5
oseltamivir	J05AH02	6.4.3
oxaliplatin	L01XA03	8.2.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN01	1.1.1; 1.4
oxytocin	H01BB02	22.3
paclitaxel	L01CD01	8.2.1
p-aminosalicylate sodium	J04AA01	6.2.5
pancreatic enzymes	A09AA02	7, 17
paracetamol	N02BE01	2.1; 5.1.5.1
paromomycin	A07AA06	6.5.2
pegaspargase	L01XX24	8.2.1
pegfilgrastim	L03AA13	8.2.3
pembrolizumab	L01FF02	8.2.3
penicillamine	M01CC01	4.2; 29.2
pentamidine	P01CX01	6.5.4; 6.5.5.1
perindopril + amlodipine + indapamide	C09BX01	12.3
permethrin	P03AC04	13.5
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5.1.1
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5.1.1

Medicine or item as in EML	ATC code	Section
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
piperacillin + tazobactam	J01CR05	6.2.2
platelets	B05AX02	11.1
plazomicin	J01GB14	6.2.3
pneumococcal vaccine	J07AL01	19.3
podophyllum resin	D06BB04	13.4
poliomyelitis vaccine	J07BF	19.3
polymyxin B	J01XB02	6.2.3
poractant alfa	R07AA	22.7
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II) · $2H_2O$	V03AB31	4.2
potassium iodide	D08AG03	6.3
potassium iodide	V03AB21	18.7
potassium permanganate	D08AX06	13.2
povidone iodine	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3; 6.1.4
prednisolone	H02AB06	3; 5.1.1; 5.1.5.3; 8.2.4; 18.1
prednisolone	S01BA04	21.2
pretomanid	J04AK08	6.2.5
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2.1
progesterone vaginal ring	G02BB02	22.1.6
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	5.1.5.2
propylthiouracil	H03BA02	18.7
prostaglandin E1	C01EA	22.7
protamine sulfate	V03AB14	10.2
pyrantel	P02CC01	6.1.1

Medicine or item as in EML	ATC code	Section
pyrazinamide	J04AK01	6.2.5
pyridostigmine	N07AA02	5.2.2; 20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quetiapine	N05AH04	24.2.2
quinine	P01BC01	6.5.3.1
rabies vaccine	J07BG	19.3
raltegravir	J05AJ01	6.4.2.4
ranitidine	A02BA02	17.1
rasburicase	V03AF07	8.2.5
ravidasvir	–	6.4.4.2.1
ready-to-use therapeutic food	–	9
realgar-Indigo naturalis formula	–	8.2.1
red blood cells	B05AX01	11.1
resin-based composites	–	30
respiratory syncytial virus vaccine	J07BX05	19.3
retinol	A11CA01	27
ribavirin	J05AP01	6.4.4.2.3
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.5
rifampicin	J04AB02	6.2.4; 6.2.5
rifapentine	J04AB05	6.2.5
risperidone	N05AX08	24.1
ritonavir	J05AE03	6.4.2.3
rituximab	L01FA01	5.1.2; 8.2.2
rotavirus vaccines	J07BH	19.3
rubella vaccines	J07BJ	19.3
salbutamol	R03AC02	25.1
salicylic acid	D01AE12	13.4

Medicine or item as in EML	ATC code	Section
selenium sulfide	D01AE13	13.1
semaglutide	A10BJ06	18.5.2
senna	A06AB06	2.3; 17.4
sevoflurane	N01AB08	1.1.1
silver diamine fluoride	–	30
silver sulfadiazine	D06BA01	13.2
simvastatin	C10AA01	12.6
sodium calcium edetate	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium hydrogen carbonate	B05XA02	26.2
sodium lactate compound solution	–	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside	C02DD01	12.3
sodium stibogluconate	P01CB02	6.5.2
sodium thiosulfate	V03AB06	4.2; 13.1
sofosbuvir	J05AP08	6.4.4.2.1
sofosbuvir + velpatasvir	J05AP55	6.4.4.2.1
spectinomycin	J01XX04	6.2.1
spironolactone	C03DA01	12.4; 16
streptokinase	B01AD01	12.5.2
streptomycin	J01GA01	6.2.5
succimer	–	4.2
sulfadiazine	J01EC02	6.5.4
sulfadoxine + pyrimethamine	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.1; 6.5.4
sulfasalazine	A07EC01	17.3; 29.2
sumatriptan	N02CC01	5.1.5.1; 5.1.5.3
sunscreen	D02BA	13.7
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tacrolimus	L04AD02	8.1

Medicine or item as in EML	ATC code	Section
tamoxifen	L02BA01	8.2.4
telmisartan + amlodipine	C09DB04	12.3
telmisartan + hydrochlorothiazide	C09DA07	12.3
tenofovir disoproxil fumarate	J05AF07	6.4.2.1; 6.4.4.1.1
terbinafine	D01AE15	13.1
testosterone	G03BA03	18.2
tetanus vaccine	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thalidomide	L04AX02	8.2.3
thiamine	A11DA01	27
tick-borne encephalitis vaccine	J07BA01	19.3
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2.1
tiotropium	R03BB04	25.1
tranexamic acid	B02AA02	10.2; 22.6
trastuzumab	L01FD01	8.2.2
triamcinolone hexacetonide	H02AB08	29.3
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.1
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)	V04CF01	19.1
typhoid vaccine	J07AP	19.3
ulipristal	G03AD02	22.1.1
urea	D02AE01	13.4; 13.6
ustekinumab	L04AC05	13.4
valganciclovir	J05AB14	6.4.3
valproic acid (sodium valproate)	N03AG01	5.1; 24.2.2

Medicine or item as in EML	ATC code	Section
valsartan + amlodipine + hydrochlorothiazide	C09DX01	12.3
vancomycin	A07AA09	6.2.2
vancomycin	J01XA01	6.2.2
varenicline	N07BA03	24.5
varicella vaccines	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	5.1.5.3; 12.1; 12.2
vinblastine	L01CA01	8.2.1
vincristine	L01CA02	8.2.1
vinorelbine	L01CA04	8.2.1
voriconazole	J02AC03	6.3
warfarin	B01AA03	10.2
water for Injection	V07AB	26.3
whole blood	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccine	J07BL01	19.3
zidovudine	J05AF01	6.4.2.1
zinc sulfate	A12CB01	17.5.2
zoledronic acid	M05BA08	8.2.5

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

WHO electronic Essential Medicines List (eEML) World Health Organization (2025)
https://list.essentialmeds.org/

WHO AWaRe (Access, Watch, Reserve) classification of antibiotics for evaluation and monitoring of use (2025)
https://iris.who.int/handle/10665/382244

The WHO AWaRe (access, watch, reserve) antibiotic book (2022)
https://iris.who.int/handle/10665/365237

Selection of essential medicines at country level. Using the WHO Model List of Essential Medicines to update a national essential medicines list (2019)
https://iris.who.int/handle/10665/330898

The selection and use of essential in vitro diagnostics: report of the fourth meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2022 (including the fourth WHO model list of essential in vitro diagnostics)
https://iris.who.int/handle/10665/373322

Selection of essential in vitro diagnostics at country level: using the WHO Model List of Essential in Vitro Diagnostics to develop and update a national list of essential in vitro diagnostics.
https://iris.who.int/handle/10665/343385

Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 700.12: operative paragraph 2.9 on pricing approaches and their impacts on availability of medicines for the prevention and treatment of cancer (2018)
https://iris.who.int/handle/10665/277190

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Third edition (2023)
https://iris.who.int/handle/10665/374250

WHO guideline on the use of glucagon-like peptide-1 (GLP-1) therapies for the treatment of obesity in adults. Version 1.1 (2025)
https://app.magicapp.org/#/guideline/LrRxrL

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This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children. It contains a summary of the evidence presented and the Committee's consideration, justifications and recommendations for additions, deletions and changes to medicines on the Model Lists.