SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Midrid 325 mg/65 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 325.0 mg

Isometheptene mucate 65.0 mg

3 PHARMACEUTICAL FORM

Capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of migraine and other vascular headaches.

4.2 Posology and method of administration

For oral administration

Adults:	2 capsules at once, then 1 capsule every hour until relief obtained up to a maximum of 5 capsules within a 12 hour period.
Children:	Not recommended.

4.3 Contraindications

Severe cardiac, hepatic or renal impairment, severe hypertension, glaucoma. Patients on monoamine oxidase inhibitor therapy. Porphyria. Hypersensitivity to paracetamol and/or other constituents.

4.4 Special warnings and precautions for use

Cardiovascular disease, diabetes mellitus, hyperthyroidism. When used in patients with high spinal cord lesions, isometheptene, like other sympathomimetics may cause autonomic dysreflexia.

Women who have recently given birth may be at increased risk of developing cerebral vasospasm following use of vasospastic agents. Women should not take Midrid during the post-partum period as there have been several reports of life- threatening cerebral vasoconstriction or intracranial haemorrhage occurring after ingestion of therapeutic doses of isometheptene during the first few weeks after childbirth.

Care is advised in the administration of this product to patients with renal or hepatic impairment. The hazards of paracetamol overdose are greater in those with non- cirrhotic alcoholic liver disease.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic

alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Do not exceed the recommended dose.

If symptoms persist consult your doctor.

Keep out of the sight and reach of children.

Patient information leaflet warning.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

Label warning:

Do not take with any other paracetamol-containing products. Immediate medical advice should be sought in the event of an overdose, even if you feel well.

4.5 Interaction with other medicinal products and other forms of interaction

On theoretical grounds, care should be taken with patients receiving cardiac glycosides, quinidine, anti-hypertensives and tricyclic anti-depressants. Alcohol reduces liver capacity to deal with paracetamol. Colestyramine reduces absorption of paracetamol. Metoclopramide and domperidone accelerate absorption of paracetamol.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

May interact with chloramphenicol, causing increased plasma levels.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

There is an increased risk of toxicity with bromocriptine & isometheptene.

There is an increased risk of a hypertensive crisis when sympathomimetics are given with MAOIs.

4.6 Fertility, pregnancy and lactation

There is no evidence of the product's safety in human pregnancy nor is there evidence from animal work that it is free from hazard. Avoid in pregnancy and lactation.
Midrid should not be taken during the post-partum period (see section 4.4).

4.7 Effects on ability to drive and use machines

No information.

4.8 Undesirable effects

Transient dizziness may appear in hypersensitive patients. This can usually be eliminated by reducing the dose. Circulatory disturbances may occur.

Adverse effects of paracetamol are rare but hypersensitivity reactions including skin rashes may occur. Anaphylaxis, angioedema, urticaria and very rare cases of fixed drug eruption have been reported. There have been reports of blood dyscrasias including

thrombocytopenia purpura and agranulocytosis, but these were not necessarily causally related to paracetamol.

Blood disorders have also been reported with isometheptene-containing products.

Metabolism and nutrition disorders: High anion gap metabolic acidosis with frequency "Not known" (cannot be estimated from the available data).

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Isometheptene

Limited information is available regarding overdose. There have been reports of cerebrovascular vasoconstriction or intracranial haemorrhage following overdose or use of excessive amounts of isometheptene-containing products.

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

or

b, Regularly consumes ethanol in excess of recommended amounts. or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not

reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N- acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24 h from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is an effective analgesic and antipyretic agent but has only weak anti-inflammatory properties. Its mechanism of action is not fully understood as it is only a weak inhibitor of prostaglandin biosynthesis, but it has been suggested that it is more effective against enzymes in the CNS than those in the periphery. The drug has no effect on the cardiovascular and respiratory systems, and it does not cause gastric irritation or bleeding like salicylates.

Isometheptene mucate is a sympathomimetic agent believed to act in migraine headache by a sympathetic activation to close arteriovenous anastomoses felt to contribute to the pain of migraine.

5.2 Pharmacokinetic properties

Isometheptene mucate is rapidly excreted in man. Excretion peaks at 2-6 hours after dosing.

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination
half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdosage and cause liver damage.

5.3 Preclinical safety data

There are no other data of relevance to the prescriber which are not included on the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Talc
Colloidal silicon dioxide

Capsule shell:
Gelatin
Water
Titanium dioxide
Erythrosine
Quinoline yellow
Indigotine
Printing ink Opacode black S-1-8100HV

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Strips of 5 or 15 capsules

Blister packs of 5, 10, 15, 20 and 30 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

DHP Healthcare Limited
13 Hanover Square
London
W1S 1HN
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00111/0205

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 September 2004

Renewed: 19 December 2007

10 DATE OF REVISION OF THE TEXT

02/02/2025