National guideline: Voxelotor for the treatment of haemolytic anaemia in sickle cell disease

Indication: Voxelotor is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) [all genotypes] in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide

Approvals: Approval from a Haemoglobinopathy Coordinating Centre (HCC) multidisciplinary team meeting should be in place prior to starting this treatment. Following approval, delivery of treatment can be undertaken at a Specialist Haemoglobinopathy Team (SHT) or a Local Haemoglobinopathy Team (LHT).

Funding: Initial funding via the Innovative Medicines Fund (IMF), with transfer to routine commissioning 30 days after the publication of NICE Final Draft Guidance (Blueteq form must be completed by HCC or SHT prior to initiating)

Eligibility criteria:

- Patient is 12 years and over*
- Patient has haemolytic anaemia due to SCD
- Patient is ineligible for, or intolerant of hydroxycarbamide, or hydroxycarbamide alone is insufficiently effective

*Voxelotor has not been studied in patients >65 years but this does not preclude use in this age group. Patients should be considered for treatment with voxelotor on an individual basis

Regimen details: 1500mg (3x500mg tablets) once daily orally

Duration of treatment: Until unacceptable toxicity or treatment failure

Administration: Voxelotor film-coated tablets should be swallowed whole with water. Voxelotor can be taken with or without food. Tablets should not be cut, crushed, or chewed because of the unpleasant taste

Missed doses

If a dose is missed, treatment should be continued on the day following the missed dose

Supportive medication: None expected - review requirement on an individual basis and prescribe as per local formulary

Regular investigations:

Haemoglobin
Reticulocyte count & percentage
Unconjugated (indirect) bilirubin
Lactate dehydrogenase
Urea & electrolytes

(To be carried out prior to initiating treatment. Frequency thereafter at prescriber's discretion)

Dose modifications:

Renal impairment

No dose adjustment is recommended in patients with mild to severe renal impairment. Voxelotor has not been evaluated in patients with end stage renal disease requiring dialysis.

Hepatic impairment

No dose adjustment of voxelotor is recommended for patients with mild or moderate hepatic impairment. The recommended dose of voxelotor in patients with severe hepatic impairment (Child Pugh C) is 1,000 mg (two 500 mg film-coated tablets) taken once daily.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed.

Drug interactions:

Concomitant use of strong CYP3A4 inducers with voxelotor should be avoided due to the risk of decreased efficacy of voxelotor. Co-administration of voxelotor with sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. If concomitant use is unavoidable, consider dose reduction of the CYP3A4 substrate(s). In vitro studies indicated that voxelotor acts as an inhibitor and inducer of CYP2B6. The clinical relevance is currently unknown, and caution is recommended when co-administering voxelotor with sensitive substrates of CYP2B6. Voxelotor is an *in vitro* inhibitor of CYP2C8, CYP2C9, and CYP2C19 at maximal systemic concentrations. Caution is recommended when co-administering voxelotor with sensitive substrates of CYP enzymes. *In vitro* studies indicated that voxelotor may act as an inhibitor of OATP1B1, OAT3 and MATE1 transporters. Therefore, caution is recommended when co-administering voxelotor with sensitive substrates of these transporters, especially for those substrates with a narrow therapeutic index.

Toxicities:

The most common adverse reactions include headache (31.8%), diarrhoea (22.7%) and abdominal pain (22.7%). Dose modifications due to an adverse reaction (including rash, diarrhoea, headache, nausea, abdominal pain and drug hypersensitivity) occurred in 13.6% of patients who received voxelotor in the pivotal study. The table below lists adverse drug reactions that occurred in patients treated with voxelotor 1,500 mg study, as well as adverse reactions from post-marketing experience.

Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available clinical study data).

System organ class	Adverse reactions[a]	Frequency category
Immune system disorders	Drug hypersensitivity	Uncommon
Nervous system disorders	Headache	Very common
Gastrointestinal disorders	Diarrhoea Abdominal pain[b] Nausea	Very common
Skin and subcutaneous tissue disorders	Rash[c]	Very common
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known

[a.] Adverse reactions were NCI Grades 1 or 2 except for Grade 3 diarrhoea (n=1), nausea (n=1), rash (n=1), rash generalized (n=3) and hypersensitivity (n=1).

[b.] Abdominal pain includes abdominal pain, abdominal pain upper, and abdominal pain lower.

[c.] Rash includes rash, urticaria, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash papular.

Comments:

Hypersensitivity reactions

Hypersensitivity to the active substance or to any of the excipients listed. Serious hypersensitivity reactions have been observed in < 1% of patients treated with voxelotor in clinical studies. Clinical manifestations may include generalised rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia.

If hypersensitivity reactions occur, voxelotor must be discontinued and appropriate medical therapy must be administered. Voxelotor must not be reinitiated in patients who experience these symptoms with previous use.

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity, which can be life-threatening or fatal, has been reported in association with voxelotor

On treatment initiation, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, voxelotor should be withdrawn immediately and an alternative treatment considered. If the patient has developed a serious reaction such as DRESS with the

use of voxelotor, treatment with voxelotor must not be restarted in this patient at any time.

Pregnancy

There are no or limited amount of data from the use of voxelotor in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid use of voxelotor during pregnancy.

In addition, all adverse pregnancy events should be reported via the Yellow Card Scheme at: https://yellowcard.mhra.gov.uk/

Breast-feeding

It is unknown whether voxelotor/metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of voxelotor in milk and subsequent uptake in pups. A risk to the new-borns/infants cannot be excluded. Voxelotor should not be used during breast-feeding.

Fertility

No human data are available on the effect of voxelotor on fertility. In rats, effects on sperm motility and morphology were observed. These effects did not, however, affect the reproductive performance. Relevance to human is not known.

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: https://yellowcard.mhra.gov.uk/

Laboratory test interference:

Voxelotor administration may interfere with measurement of haemoglobin (Hb) subtypes (HbA, HbS, and HbF) by high-performance liquid chromatography (HPLC). If precise quantitation of Hb species is required, chromatography should be performed when the patient has not received voxelotor therapy in the immediately preceding 10 days.

References:

National Institute for Health and Care Excellence, 2024. *Final draft guidance: Voxelotor for treating haemolytic anaemia caused by sickle cell disease* [Online] Available at: https://www.nice.org.uk/guidance/gid-ta10505/documents/674-3 [Accessed 13th May 2024]

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Vichinsky, E., et al, 2019. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *N Engl J Med* [Online], 381(6) Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1903212 [Accessed 13th May 2024]

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