Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

mhra.gov.uk

Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Voxelotor is indicated for the treatment of hemolytic anemia (haemoglobin ≤ 10.5 g/dL) in adult and pediatric patients 12 years and older with sickle cell disease (SCD). Voxelotor can be administered alone or in combination with hydroxycarbamide.

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising unlicensed medicines to UK patients that have a high unmet clinical need. A positive scientific opinion is only issued by the MHRA if the criteria for the EAMS are fulfilled, which includes demonstrating a positive benefit risk balance (quality, safety and efficacy assessment) and the ability of the pharmaceutical company to supply a medicine according to a consistent quality standard.

EAMS medicines are unlicensed medicines. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. GMC guidance on prescribing unlicensed medicines can be found below:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

The opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a licensed indication or a future commitment by the MHRA to licence such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

EAMS procedural assessment at the MHRA

A full assessment of the quality, safety and efficacy of [product INN or code number] has been conducted by the MHRA's assessment teams, including pharmacists, toxicologists, statisticians, pharmacokinetic and medical assessors. This assessment process also includes consideration of the quality, safety and efficacy aspects by the UK independent expert committees including Expert Advisory Groups (EAGs) and the Commission on Human Medicines (CHM):

- The Commission on Human Medicines (CHM) advises ministers on the quality, safety and efficacy of medicinal products. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies. The Chair and Commissioners follow a code of practice, in which they are precluded from holding personal interests. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine.

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about

- Chemistry, Pharmacy and Standards EAG, which advises the CHM on the quality in relation to safety and efficacy of medicinal products

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#chemistry-pharmacy-and-standards-eag

Pharmacovigilance system

A pharmacovigilance system for the fulfilment of pharmacovigilance tasks has been put in place for this EAMS medicine, including a risk management plan. As the safety profile of the EAMS medicine is not fully established it is particularly important that any harmful or unintended responses to EAMS medicines are reported. Healthcare professionals should be aware of their obligations to report adverse event information upon enrolment of any patients receiving EAMS medicines in the scheme. They will be required to follow the process which the pharmaceutical company which manufactures the EAMS medicine has in place to enable systematic collection of information on adverse events.

For more detailed information on this EAMS medicine, please refer to the Public Assessment Report, EAMS treatment protocol for healthcare professionals, EAMS treatment protocol for patients and EAMS treatment protocol for pharmacovigilance.

https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

Justification for the fulfilment of the EAMS criteria

There are four EAMS criteria that need to be fulfilled before a medicine can enter the scheme and a positive scientific opinion is issued by the MHRA. The fulfilment of the criteria for this particular medicine is described below.

1	**(a) Life threatening and seriously debilitating condition** In the UK, SCD affects about 1 in 2000 live births, and there are currently estimated to be about 12,500 individuals living with SCD. • SCD patients have a variable degree of anaemia due to ongoing intravascular and extravascular haemolysis. • In the steady state, individuals with sickle cell anaemia and sickle cell/β0 thalassaemia will usually have a low Hb concentration (60-90 g/l). • Fatigue is increasingly being described as a significant symptom for patients with SCD and may be associated with chronic anaemia, even if this is stable. • Patients may tolerate their anaemia for many years but with increasing age and co-morbidities (eg, cardiac or respiratory disease) may develop symptomatic anaemia despite a stable Hb. • A rapid, significant fall in Hb, usually of at least 20 g/l, may result in the individual becoming symptomatic and major reductions may lead to cardiovascular compromise. • Acute anaemia in SCD may be due to an increase in haemolysis, eg, due to a transfusion reaction, infection or glucose-6-phosphate dehydrogenase deficiency, reduction in erythropoiesis, blood loss and sequestration, in the spleen and less commonly in the liver. The chronic haemolytic anaemia of SCD leads to reduced oxygen carrying capacity, reduced oxygen delivery, tissue hypoxia, and cumulative organ damage, especially in organs sensitive to ischemia (brain, heart, kidney). When chronic haemolytic anaemia in SCD is compounded by acute anaemic episodes, devastating organ damage can occur due to failure of compensatory physiologic mechanisms (eg, increased blood flow, cerebral vasodilation). Symptomatic haemolytic anaemia leads to reduced oxygen carrying capacity and tissue hypoxia that causes severe fatigue and negatively impacts day to day activity and quality of life of SCD patients, including depression,

	missed school/work, etc. Acute anaemic episodes can occur for several reasons, including increased haemolysis related to VOCs, acute splenic sequestration, transient red cell aplasia, and hyperhaemolysis due to transfusion reactions. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Current recommendations for treatment of patients with SCD include the following available options: hydroxyurea (HU), transfusions, and erythropoietin for symptomatic treatment and bone marrow transplant. More recently Adakveo® (crizanlizumab) has been approved for the prevention of vaso-occlusive crises (VOCs). Importantly, however, there is currently no EU or GB approved therapy for the treatment of haemolytic anaemia associated with SCD. Therefore, there is an unmet need in significant number of patients who do not respond adequately to currently available treatments or in whom these treatments cannot be administered due to intolerability.
2	**The medicinal product offers major advantage over existing methods in the UK** In the pivotal phase 3 study GBT440-031, 274 patients were randomized. The primary endpoint was hemoglobin (Hb) response which was defined by an increase of Hb from baseline by > 1 g/dL at 24 weeks. The results of the exact CMH general association test for Hb response rate at Week 24, are as follows: In the ITT Population, 51.1% (46/90) of the subjects in the voxelotor 1500-mg group and 32.6% (30/92) of the subjects in the voxelotor 900-mg group achieved a > 1 g/dL increase in Hb from Baseline to Week 24, compared with 6.5% (6/92) of the subjects in the placebo group. These results are in favor the target dose of 1500mg. The difference in the adjusted response rate at Week 24 for voxelotor 1500 mg vs placebo was 45.0% (95% CI: 33.4% to 56.7%) and statistically significant ($p < 0.001$). For voxelotor 900 mg vs placebo, the difference in the adjusted response rate at Week 24 was 26.4% (95% CI: 15.5% to 37.3%; $p < 0.001$). The primary endpoint was met. The following secondary endpoints supported the primary endpoint: - Change from Baseline in Hemoglobin at Week 24: the difference between voxelotor 1500-mg and placebo was 1.23 g/dL (95% CI: 0.86 to 1.60 g/dL) and statistically significant ($p < 0.001$), and the difference between the voxelotor 900-mg and placebo was 0.68 g/dL (95% CI: 0.31 to 1.04 g/dL; $p < 0.001$). - Change and Percentage Change From Baseline in indirect Bilirubin and Reticulocyte Percentage, at Week 24: differences in the LS mean percentage change from Baseline between the voxelotor 1500-mg group and placebo group were -26.4% (95% CI: -36.1% to -16.6%;$p < 0.001$) for indirect bilirubin, -24.8% (95% CI: -37.9% to -11.6%; $p < 0.001$) for reticulocyte percentage The clinical complications of SCD result from a cascade of events that starts with the polymerization of HbS. Thus, the goal of disease-modifying therapies is to decrease Hgb S concentration, either by increasing HbF levels (HU) or increasing HbA levels (transfusion). Curative options, such as hematopoietic stem cell transplantation (HSCT) and gene therapy, strive to eliminate the production of HbS. Supportive therapies, such as antibiotic prophylaxis, have increased survival of children by preventing death from overwhelming infection, but have not increased overall life expectancy for people living with SCD. With the increasingly widespread use of disease-modifying and curative therapies, the life expectancy will increase and

	approach that of the average affected British patients. Voxelotor offers an improvement over existing therapies in the UK.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** Overall, patients with SCD in Studies GBT440-031 (HOPE), GBT440-034, GBT440-007 Parts A and B, GBT440-001, GBT440-024, expanded access program (EAP) GBT440-037, and the collection of single patient eIND protocols have been exposed for a total of 365.2 patient years with daily doses of voxelotor. Patients with SCD in Study GBT440-031 have been exposed to voxelotor for 107.2 patient years with the 900 mg dose and 98.3 patient years with the 1500 mg dose. Paediatric patients in Study GBT440-007 Part B have been exposed to voxelotor for 10.7 patient years with the 900 mg dose and 6.2 patient years with the 1500 mg dose. Across all 25 studies in the voxelotor clinical development program, the overall incidence of TEAEs leading to study drug discontinuation was low, and the most commonly reported serious adverse events (SAEs) were predominantly assessed by the investigator as not related to study drug. Across all studies in SCD patients, the incidence of study drug discontinuations due to TEAEs was ≤10% and the incidence of study drug-related SAEs was <5%. There were a total of 12 deaths of which 6 occurred in the HOPE study (2 subjects in each of the treatment groups) and 6 across the other studies, none of which were assessed by the investigator as related to study treatment. As with adults, the most commonly reported SCD related TEAEs across all treatment groups in paediatric patients from Studies GBT440-031 and GBT440-007 Part B was sickle cell anaemia with crisis. Overall, the identified ADRs were mostly low grade in severity and clinically manageable and the AE safety profile in the clinical development program was similar between paediatric patients and adult patients. Provided the outstanding issues are satisfactorily resolved, the risk benefit in principle can be deemed positive.
4	**The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.** The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.