National Haemoglobinopathy Panel

Voxelotor National SOP

Further to the designation of Promising Innovative Medicine (PIM) status for voxelotor in May 2021 (EAMS Step 1), MHRA issued a positive Scientific Opinion on 25th January 2022 which supports voxelotor for: "the treatment of haemolytic anaemia in adults and paediatric patients 12 years of age and older with sickle cell disease (SCD)".

Voxelotor in the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide is available as part of an Early Access to medicines Scheme (EAMS).

Eligibility criteria for use within the EAMS*:

Inclusion Criteria:

Patients who meet all the following criteria will be eligible for inclusion in this programme:

1. 12 years of age and older. Willing and able to provide written informed consent (age ≥ 16 years) or legal representative consent (age 12 - 15 years), as required per institution and local regulations

2. Documented diagnosis of SCD (all genotypes)

3. Evidence of haemolytic anaemia associated with SCD (Hb ≤ 105 g/L) and one or more of the following

    3a: Haemolytic phenotype (i.e., leg ulcers, priapism, pulmonary hypertension) who are untransfusable or very difficult to transfuse due to previous transfusion reactions or significant alloimmunisation or not consenting to regular blood transfusions

    3b. Poor response (on maximum tolerated dose) or toxicity to hydroxycarbamide (HC) or not consenting to HC

    3c. Symptomatic of anaemia (i.e., hypoxia, fatigue, worsening cardiac function, poor performance status) who cannot be transfused as in 3a

4. If patients taking HC, the dose of HC (mg/kg) must be stable for at least 3 months prior to participation in EAMS

Exclusion Criteria:

Patients who meet any of the following criteria will not be eligible for inclusion in this programme:

1. History of hypersensitivity reaction to voxelotor or excipients

2. Pregnancy or breastfeeding

3. Hepatic dysfunction characterised by alanine aminotransferase > 4 times upper limit of normal

4. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; < 30 mL/min/1.73m^2 or on dialysis

5Haemoglobin >105 g/l

6. Participated in another clinical trial of an investigational agent (within 30 days of participation in EAMS)

7. Medical, psychological, or behavioural conditions, which, in the opinion of the treating physician, makes patient unsuitable to participate in this programme

8. Significant drug interactions with voxelotor.

9. Active malignancies

10. On transfusion programme for stroke prevention

Exceptionality

Addition of Crizanlizumab to Voxelotor treatment should be discussed at the NHP MDT and approved there if to proceed.

Guideline for the use of Voxelotor for treatment of haemolytic anaemia in sickle cell disease

Indication: 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

Funding: EAMS SSC2339 – Blueteq form must be completed along with registration on Inceptua portal

Regimen details: 1500mg (3x500mg tablets) once daily orally, or lower if toxicities

Frequency: Daily treatment

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

Pre-medication: Non-applicable

Anti-emetics: Review requirement on an individual basis and prescribe as per local policy

Supportive medication: Non-applicable

Regular investigations: Haemoglobin, Reticulocyte count/%, Bilirubin including total bilirubin and conjugated and unconjugated bilirubin, Lactate dehydrogenase
All investigations 2weekly x 2 and then monthly x 3-6 then every 3 months once stable (no side effects)

Standard limitations to go ahead: (as per inclusion and exclusion criteria)

Dose modifications: *Renal impairment*
No dose adjustment is recommended in patients with mild or moderate renal impairment. Patients with severe renal impairment or End Stage Renal Disease) ESRD requiring dialysis are excluded from this EAMS

Hepatic impairment

No dose adjustment of Voxelotor is recommended for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment are excluded from this EAMS (characterised by alanine aminotransferase (ALT) >4 × upper limit of normal
Dose reduction to 1000mg with child Pugh score of 3

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed

Toxicities:

Adverse reactions	Voxelotor 1500mg	Placebo
Headache	31.8%	25.3%
Diarrhoea	22.7%	11%
Pain	17%	19.8%
Nausea	19.3%	9.9%
Arthralgia	21.6%	14.3%

Comments:

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, we advise avoiding the use of voxelotor during pregnancy.

Reporting Pregnancy

If a patient or a partner pregnancy is identified during the course of the study (retrospective or prospective review) while taking voxelotor, the pregnancy should be reported to GBT pharmacovigilance (globalbloodtx@primevigilance.com) immediately.

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

Voxelotor will be discontinued immediately.

Reported pregnancy of a patient or a patient's partner, while participating in EAMS, will be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (i.e. birth or spontaneous or elective abortion), if a patient or a patient's partner consent for follow-up. The child born to a female patient or partner of a male patient exposed to voxelotor will be followed for 3 months after delivery.

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

· The reporting of an adverse event will be within 24 hours and no later than 1 working day of awareness using the 'Voxelotor EAMS Adverse Event Reporting Form' available in the IMAP portal for voxelotor´ s EAMS programme.

· Physicians will complete the 'Voxelotor EAMS Adverse Event Reporting Form' and send it directly by email to globalbloodtherapeutics@parexel.com cc: drugsafety@gbt.com or Fax Form to:+1 650.243.3433

· A unique identifier will be generated by Inceptua once an individual patient is accepted into the EAMS scheme. The unique identifier will be used to track and deliver voxelotor to the hospital pharmacy and will also be used for monitoring safety information. This number will remain in a database of patients entered into EAMS. If a patient enrols in EAMS but does not receive treatment, the unique identifier will not be reused.

· AE reports will be followed-up by GBT´s pharmacovigilance department which will contact the participating physician as necessary in order to obtain supplementary detailed information significant for the scientific evaluation of the case. The data management of all AE/safety information will be in accordance with GBT´s pharmacovigilance procedures.

· Pharmacovigilance data will be captured throughout the scheme until the end of EAMS for patients with reported events. For patients who withdraw from the EAMS programme, GBT´s UK Medical Affairs Team will make every effort to obtain further information for up to 3 months after withdrawal.

· GBT will produce a 3-monthly periodic report of all AE reports received via the EAMS scheme, the first data lock point (DLP) will be 3 months from the date of scientific opinion. Submission of the report will be 1-month post DLP. The 3 monthly reports will

continue until the end of the EAMS scheme with a final report to be submitted 1 month after the expiry of the EAMS scientific opinion.

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.

Drug interactions: Refer to EAMS Treatment protocol, available at: Voxelotor: Treatment protocol: Information for healthcare professionals - GOV.UK (www.gov.uk)

References:

Voxelotor: Treatment Protocol: Information for Healthcare professionals. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050835/Voxelotor_Treatment_protocol_Information_for_healthcare_professionals.pdf

Voxelotor prescribing information FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213137s006lbl.pdf

Prepared by: Anish Tailor	Checked by:
Consultant approval:	Approving body: Date:
Version: 1.0	Review date:

HCC Trust Logo

Appendix 1 - HCC MDT Proforma for approval of Voxelotor

Date of HCC MDT:	Responsible Consultant:
Referring centre:	Referring clinician (if different from above)
Patient name:	Date of birth:
NHS number:	Diagnosis:
GP details inc. code:	

Eligibility criteria of managed access agreement:
Patient discussed by referring clinician at local MDT and agreed suitable for Voxelotor☐
Date of local MDT:……
Confirmed diagnosis of sickle cell disease ☐
Aged 12 or over ☐
Addition of Crizanlizumab treatment should be discussed at NHP MDT

Is the patient receiving regular blood transfusion?	YES/NO
Most recent Haemoglobin value	
Baseline Haemoglobin (Average value in past 6 months)	
Most recent reticulocyte count	
Most recent bilirubin	
Most recent LDH	
Number of transfusion related admissions in past 12 months (excluding those for stroke prevention)	
Number of red blood cell units transfused in past 12 months	
Number of VOC in past 12 months	
Number of ACS in past 12 months	
Pulmonary Hypertension?	
Signs of kidney impairment/low function capacity	
Number of emergency visits related to SCD in past 12 months	
Is the patient registered on the NHR? (required to submit data)	YES/NO

Please state other relevant information to support application e.g. complications of sickle cell disease, previous treatment:

MDT discussion:

MDT outcome:
Approved ☐
Not approved ☐
Further information required (please specify) ☐