National Haemoglobinopathy Panel

Crizanlizumab National Guideline

NICE has recommended Crizanlizumab as a treatment option for preventing recurrent crises (vaso-occlusive crises, VOCs) in people aged 16 or over with sickle cell disease (SCD). The recommendation is based on analysis of data from the SUSTAIN trial. The conditions described in the managed access agreement (MAA, NICE TA743) must be followed. Crizanlizumab can be given as an add-on therapy to hydroxycarbamide or as a monotherapy in patients for whom hydroxycarbamide is inappropriate or inadequate.

Eligibility criteria for use within the MAA*:

- Patient has a confirmed diagnosis of sickle cell disease (SCD), any genotype
- Patient is aged 16 and over
- Patient has had 2 or more confirmed VOCs in the previous 12 months, defined as an acute painful episode that requires pain relief medication to manage at home or in hospital
- Application for treatment is made by a Specialised Haemoglobinopathy Team (SHT) having been discussed and approved by the Haemoglobinopathy Coordinating Centres (HCCs) MDT prior to initiation of treatment (see Appendix 1 for MDT proforma)

*The terms of the MAA were agreed based on the assumption that:

- All people with SCD would have been offered or had hydroxycarbamide for at least 6 months and it has not adequately reduced VOCs or is inappropriate before being considered for crizanlizumab AND
- People are unlikely to have crizanlizumab alongside regular blood transfusions to prevent recurrent VOCs. People having regular blood transfusions were excluded from the SUSTAIN trial

NHS England requirements:

Patients must meet the criteria as specified in the MAA and must not be receiving regular blood transfusions.

National Haemoglobinopathy Registry (NHR) requirement:

Under the terms set out in the MAA, it is the responsibility of the patients' healthcare team at the treating centre to enter data in to the NHR including, but not limited to, hydroxycarbamide use, VOC event and location in which the VOC was managed e.g. emergency department, home.

Guideline for the use of crizanlizumab for preventing sickle cell crises in sickle cell disease

Indication: Prevention of recurrent sickle cell crises (vaso-occlusive crises) in people aged 16 or over with sickle cell disease

Funding: NICE TA743 – Blueteq form must be completed prior to initiation of treatment

Regimen details:

Loading (week 0 and week 2)

Crizanlizumab	5mg/kg[#]	IV	D1 & D15

Maintenance (i.e. week 6 onwards)

Crizanlizumab	5mg/kg[#]	IV	Every 28 days

[#]Dose to be based on actual body weight. Doses should be rounded to measurable volumes according to local policy and prescribing platforms (the nearest 10mg is suggested but not mandated). If the patient's weight changes, the dose prescribed must be within 6% of the calculated dose.

Frequency: Loading schedule: Week 0 and Week 2

Maintenance: 4 weekly (28 days) from week 6 onwards

Duration of treatment: Until unacceptable toxicity or treatment failure

Administration: Administered in a total volume of 100ml of Sodium Chloride 0.9% or Glucose 5% by intravenous infusion over a period of 30 minutes.

Diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter.

After administration of Crizanlizumab, flush the line with at least 25 ml sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 5%.

<u>Infusion Related Reactions (IRRs)</u>
<u>See Appendix 2 for the grading of IRRs.</u>

In clinical studies, infusion-related reactions (defined as occurring during infusion or within 24 hours of the infusion) were observed in 3 patients (2.7%) treated with crizanlizumab 5 mg/kg.

Patients must be observed for IRRs for 60 minutes after the initial two infusions (i.e. Week 0 and week 2). If no IRR is observed during the initial

infusions the observation time may be reduced to 30 minutes for all further infusions.

Patients should be monitored for, and advised of, signs and symptoms of infusion-related reactions, which may include pain in various locations, headache, fever, chills, nausea, vomiting, diarrhoea, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing. **Exercise caution with corticosteroids in patients with SCD unless clinically indicated (e.g. treatment of anaphylaxis).**

Management of Infusion Related Reactions

Severity of adverse reaction	Management recommendation
Mild to moderate (Grade 1 to 2) infusion-related reactions	Temporarily interrupt or reduce the infusion rate. Initiate symptomatic treatment.* Once symptoms resolve, the infusion may be restarted at a reduced rate, and up-titrated based on tolerance. If the rate infusion is reinitiated the total time of infusion must not exceed 2 hours. For subsequent infusions, consider premedication as per local practice (e.g. antihistamines, paracetamol, IV fluids) and/or extending the infusion time to 1 hour.
Severe (≥ Grade 3) infusion-related reactions	Discontinue treatment with crizanlizumab. Initiate symptomatic treatment.*
* E.g. antipyretic, analgesic and/or antihistamine. IV fluids. Caution should be exercised with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g. treatment of anaphylaxis).	

<u>Missed doses</u>
If a dose is missed, the treatment should be administered as soon as possible according to the below guidance:

- If crizanlizumab is administered within 2 weeks after the missed dose, dosing should be continued according to the patient's original schedule.

- If crizanlizumab is administered more than 2 weeks after the missed dose, dosing should be continued every 4 weeks thereafter.

Extravasation: Non-vesicant

Pre-medication: Non-applicable

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

Supportive medication: Non-applicable

Preparation & storage: The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique. Refer to section 6.6 of the Summary of Product Characteristics for instructions on preparation.

Once prepared, if not administering crizanlizumab immediately, store the diluted solution (infusion bag/container) either:

At room temperature up to 25°C for no more than 4.5 hours:

- From the start of preparation (piercing the first vial) to the completion of infusion

Under refrigeration at 2°C to 8°C for no more than 24 hours: From the start of preparation (piercing the first vial) to the completion of infusion

- This includes the storage of the diluted solution and the time to warm up to room temperature
- Protect the diluted solution from light during storage under refrigeration

Regular investigations: Prior to cycle 1:

FBC	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
Reticulocytes	Day 1 (within 14 days)

Future investigations to be carried out as per local policy and reviewed by the responsible clinical team.

Baseline Pregnancy Test in persons of child bearing potential.

Standard limitations to go ahead:

Investigation	**Limit**
eGFR	**≥35 ml/min/1.73m^2**
Haemoglobin	**≥4.0 g/dL**

Dose modifications: It is the responsibility of the prescribing clinician to monitor the results of blood tests. No dose adjustments are recommended in mild to moderate renal impairment. The safety of crizanlizumab in patients with hepatic impairment has not been established. Crizanlizumab should *not* be given in severe hepatic impairment e.g. evidence of cirrhosis.

Contraindications: As per the SUSTAIN trial, patients are not eligible to receive crizanlizumab if there is significant active and poorly controlled (unstable) cardiovascular (including atrial or ventricular cardiac arrhythmias), neurologic, endocrine, hepatic, or renal disorders clearly unrelated to SCD.

Toxicities:

The frequency category for each adverse reaction is based on the following convention: 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 the available data).

System organ class	**Frequency**	**Adverse reaction**
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Very common	Nausea, abdominal pain*
	Common	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus*
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, back pain
	Common	Myalgia, musculoskeletal chest pain
General disorders and administration site conditions	Very common	Pyrexia
	Common	Infusion site reaction*
	Not known	Pain[#]
Injury, poisoning and procedural complications	Common	Infusion-related reaction

**The following groupings contain the preferred terms:*
- Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness

- Pruritus: pruritus and vulvovaginal pruritus

- Infusion site reaction: infusion site extravasation, infusion site pain, and infusion site swelling

[#]Pain in various locations occurring during infusion or within 24 hours of the infusion (e.g. potential infusion related reaction). This includes but is not limited to abdominal pain, arthralgia, back pain, bone pain, chest pain, general body pain, headache, muscle spasms, musculoskeletal pain, myalgia, pain in extremity.

Location of delivery: Day-case setting. Crizanlizumab can be delivered in any hospital where registered nurses are suitably trained to administer monoclonal antibodies. Availability of resuscitation equipment must be ensured as a standard precaution.

Comments: <u>Pregnancy</u>
There is a limited amount of data from the use of crizanlizumab in pregnant women. Based on data from animal studies, crizanlizumab has the potential to cause foetal harm when administered to a pregnant

woman, especially in the third trimester.As a precautionary measure, it is preferable to avoid the use of crizanlizumab during pregnancy and in woman of childbearing potential not using contraception.

To help determine the effects in pregnant women, healthcare professionals are encouraged to report all pregnancy cases and complications during pregnancy (from 105 days prior to the last menstrual period onward) to the local representative of the marketing authorisation holder (see package leaflet), in order to allow monitoring of these patients through the Pregnancy outcomes Intensive Monitoring programme (PRIM).

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 crizanlizumab is excreted in human milk after administration of Crizanlizumab. There are no data on the effects of crizanlizumab on the breast-fed newborn/infant or on milk production. Because many medicinal products, including antibodies, can be excreted in human milk, a risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue crizanlizumab therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effect of crizanlizumab on human fertility. Available non-clinical data do not suggest an effect on fertility under crizanlizumab treatment.

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: automated platelet counts
Interference with automated platelet counts (platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when tubes containing EDTA were used. This may lead to unevaluable or falsely decreased platelet counts.

There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect *in vivo*. Should unexpected

discrepancies in platelet count occur, it is recommended that blood samples are collected in citrate tubes.

Drug interactions:

Refer to summary of product characteristics, available at: https://www.medicines.org.uk/emc/

Interactions between crizanlizumab and other medicinal products have not been investigated in dedicated studies.

Monoclonal antibodies are not metabolised by cytochrome P450 (CYP450) enzymes. Therefore, medicinal products that are substrates, inhibitors or inducers of CYP450 are not expected to affect the pharmacokinetics of crizanlizumab. In clinical studies, HU/HC had no effect on crizanlizumab pharmacokinetics in patients.

No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies.

References:

Ataga et al; Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease; N Engl J Med 2017; 376:429-439

Crizanlizumab (Adakveo®) summary of product characteristics via: https://www.medicines.org.uk/emc/

National Institute for Health and Clinical Excellence (TA743) via: https://www.nice.org.uk/

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Insert HCC logo here

Appendix 1 - HCC MDT Proforma for approval of crizanlizumab

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

Eligibility criteria of managed access agreement:
Patient discussed by referring clinician at local MDT and agreed suitable for crizanlizumab ☐
Date of local MDT:……
Confirmed diagnosis of sickle cell disease ☐
Aged 16 or over ☐
2 or more confirmed VOCs in the previous 12 months[¥] ☐
Number of home VOCs: ……
Number of admissions with VOC: ……..

Is the patient currently taking hydroxycarbamide?	YES/NO
If YES, please state duration of treatment (minimum 6 months recommended to approve crizanlizumab)	
Has there been a reduction in VOCs since starting hydroxycarbamide?	YES/NO
If the patient is NOT taking hydroxycarbamide, please state reason:	
Is the patient receiving regular blood transfusion?	YES/NO
Does the patient have an eGFR ≥35ml/min/1.73m^2	YES/NO
Does the patient have evidence of *severe* hepatic impairment?	YES/NO
Does the patient have adequate venous access?	YES/NO
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) ☐

Blueteq approval number (to be completed by SHT):

[¥]VOC defined as an acute painful episode that requires pain relief medication to manage at home or in hospital

Appendix 2 – Grading Infusion Related Reactions

	Grade 1	Grade 2	Grade 3	Grade 4
Infusion- related reaction[a]	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Allergic reaction[b]	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated
Anaphylaxis[c]			Symptomatic bronchospasm with or without urticarial; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated

[a] Infusion-related reaction definition: a disorder characterised by adverse reaction to the infusion of pharmacological or biological substances.

[b] Allergic reaction definition: a disorder characterised by an adverse local or general response from exposure to an allergen.

[c] Anaphylaxis definition: a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.