Chemotherapy Protocol

Recurrent Vaso-Occlusive Crises in Sickle Cell Disease

CRIZANLIZUMAB

Regimen

- Recurrent Vaso-Occlusive Crises in Sickle Cell Disease- Crizanlizumab

Indication

- Confirmed diagnosis of Sickle Cell Disease (any genotype)
- Patient must be 16 years old or older
- Patient has had 2 or more confirmed Vaso-Occlusive Sickle Cell Crises in the last 12 months.
- Application for treatment needs to be made by a specialised haemoglobinopathy team and approved the haemoglobinopathy co-ordinating centre's MDT before treatment.
- It can be used as add on therapy for hydroxycarbamide or used as monotherapy in cases where hydroxycarbamide is inappropriate
- Patient's must not be receiving regular blood transfusions
- Blueteq form must be done for funding- NICE TA743

Toxicity

Drug	Adverse Effect
Crizanlizumab	Nausea, arthralgia, pyrexia, back pain, abdominal pain, myalgia, musculoskeletal chest pain, diarrhoea and infusion-related reactions.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, LFTs, U&Es and Reticulocytes prior to first dose
- Ongoing monitoring is then as per local policy or under clinician guidance

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following criteria must be met.

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 4g/dL (40g/L)

There is little need to adjust the dose Crizanlizumab for haematological toxicity.

N.B. Crizanlizumab has been shown to cause platelet clumping which interferes with automated platelet counts in clinical studies. Which may lead to falsely decreased platelet counts or unusable results. To try and prevent this interference, it is recommended to run the blood test as soon as possible (within 4 hours of bloods being taken). There is no evidence that crizanlizumab causes a reduction in circulating platelets.

Hepatic Impairment

The safety of crizanlizumab has not been established in hepatic impairment. Crizanlizumab should not be given in severe hepatic impairment, but no dose adjustment should be required for mild to moderate hepatic impairment.

Renal Impairment

Drug	Creatinine Clearance	Dose (% of original dose)
Crizanlizumab	≥35 ml/min/1.73m2	100%
Crizanlizumab	<35 ml/min/1.73m2	The data from patients with severe renal impairment in current studies is too limited to draw conclusions on it's use in this patient subset.

Other

Infusion related reactions were seen in 2.7% of patients in clinical studies but they have also been reported in in the post marketing setting. Most reactions have occurred within a few hours of finishing the first or second infusion of crizanlizumab, but a few reactions have occurred with a later onset of severe pain events following previous well tolerated infusions.

Patients must be observed for infusion related reactions following a crizanlizumab infusion. They should also be advised of the symptoms of an infusion related reaction to look out for. These include wheezing, shortness of breath, pain, fever, chills, sweating, headache, dizziness, vomiting, nausea, diarrhoea, uticaria, pruritus and fatigue.

Patient should be observed for 60minutes following their first two infusions. If no infusion related reaction is observed after their first two infusions, the observation time can be reduced to 30 minutes for all following infusions.

Management of Infusion Related Reactions

Severity of Reaction	Recommendations
Mild (Grade 1) to Moderate (Grade 2) Infusion Related Reactions	Temporarily interrupt or reduce infusion rate. Initiate symptomatic treatment with antipyretic, analgesic and/or antihistamine. Caution should be used with corticosteroids in patients with sickle cell disease unless clinically indicated e.g., anaphylaxis. When symptoms resolve, the crizanlizumab infusion can be restarted at a reduced rate and then up-titrated according to tolerance. If the rate infusion is re-initiated the total time of infusion must not exceed 2 hours. For subsequent crizanlizumab infusions consider using pre-medications e.g., paracetamol and chlorphenamine and/or extending the administration time to 1 hour.
Severe (≥ Grade 3) Infusion Related Reactions	Discontinue crizanlizumab treatment Initiate symptomatic treatment with antipyretic, analgesic and/or antihistamine. Caution should be used with corticosteroids in patients with sickle cell disease unless clinically indicated e.g., anaphylaxis.

Regimen

Loading doses given at Week 0 and Week 2. Then maintenance infusions given every 4 weeks thereafter until treatment failure or unacceptable toxicity.

Cycle 1- Loading (42 days)

Drug	Dose	Days	Route
Crizanlizumab	5mg/kg	Day 1 Day 15	Intravenous infusion in 100ml Sodium Chloride 0.9% or Glucose 5% over 30 minutes

Cycle 2 Onwards- Maintenance (28 day cycle)

Drug	Dose	Days	Route
Crizanlizumab	5mg/kg	1	Intravenous infusion in 100ml Sodium Chloride 0.9% or Glucose 5% over 30 minutes

Dose Information

- Dosing based on actual body weight
- Dose rounding should be done to nearest measurable volume e.g., rounded to nearest 10mg
- If the patient's weight changes, the dose prescribed should be within 6% of what the calculated dose would be.

Administration Information

Extravasation

- Crizanlizumab- non-vesicant

Other

- Diluted crizanlizumab solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter
- After administration, the line must be flushed with at least 25ml of sodium chloride 0.9% or glucose 5%.
- The standard administration time for crizanlizumab is 30 minutes, but this may be extended to a maximum of 2 hours, depending on how the patient tolerates the infusion.
- Crizanlizumab can cause an infusion related reaction, see above. Patient needs to be monitored for 1 hour after their first two infusions. If those 2 infusions are tolerated well, monitoring time can be reduced to 30 minutes.
- Once prepared by a trained healthcare professional using aseptic technique, crizanlizumab can be stored:
    - At room temperature up to 25°C, for a maximum of 4.5 hours (from first piercing of vial during preparation until the end of the infusion)
    - Or in a fridge from 2-8°C, for a maximum of 24 hours (from first piercing of vial during preparation until the end of the infusion, including time taken to warm solution to room temperature before administration) Solution should be protected from light when stored in a fridge

Additional Information

- No pre-medications, anti-emetics or supportive medications not routinely required.

- There is limited data for the use of crizanlizumab in pregnancy, but from animal studies there is potential to cause foetal harm, especially if administered in the third trimester. So as a precautionary measure crizanlizumab should be avoided in pregnant women.

References

1. Novartis Pharmaceuticals UK Ltd, 2022. *Adakveo 10 mg/ml concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc)*. [online] Medicines.org.uk. Available at: <https://www.medicines.org.uk/emc/product/12943/smpc#USEHANDLING> [Accessed 12 October 2022].
2. Rachel Lloyd & Llywelyn Cadman-Davies on behalf of the National Haemoglobinopathy Panel, 2022. *Crizanlizumab National Guideline*. [online] National Haemoglobinopathy Panel, pp.1-9. Available at: <https://www.nationalhaempanel-nhs.net/publications/xgr7p0nktidjl0s40ae5i4liuyc4p6-6ryxg> [Accessed 12 October 2022].

REGIMEN SUMMARY
Crizanlizumab

Loading Regimen, Cycle 1

Day 1

Crizanlizumab 5mg/kg intravenous infusion in 100ml Sodium Chloride 0.9% over 30 minutes

Administration Instructions
Crizanlizumab must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

Day 15

Crizanlizumab 5mg/kg intravenous infusion in 100ml Sodium Chloride 0.9% over 30 minutes

Administration Instructions
Crizanlizumab must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

Maintenance Regimen, Cycle 2 Onwards

Day 1

Crizanlizumab 5mg/kg intravenous infusion in 100ml Sodium Chloride 0.9% over 30 minutes every 28 days

Administration Instructions
Crizanlizumab must be administered via a non-PVC administration set containing an in-line 0.22 micron filter

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	November 2022	None	Beth Douse Pharmacist	Dr Srinivasan Narayanan Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.