

ISATUXIMAB WITH POMALIDOMIDE AND DEXAMETHASONE

INDICATION

Relapsed/refractory multiple myeloma after receiving 3 prior lines of therapy including lenalidomide and a proteasome inhibitor, and where patient's disease has progressed on their last treatment, as per CDF criteria. **Bluteq form is required**

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&E
 - LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Baseline random blood glucose level
 - Virology: EBV, CMV, Hep B, Hep C, HIV serology
 - Consider annual flu and 5 yearly pneumococcal vaccination pre therapy
 - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
 - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
 - Serum free light chain assay (Freelite)
 - β_2 microglobulin
 - LDH
 - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to

Wessex Regional Genetic Laboratory

Salisbury NHS Foundation Trust

Salisbury District Hospital

Salisbury

Wiltshire, SP2 8BJ

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that patient is due to commence isatuximab. Patient will require red cell phenotyping as cross match fails due to binding of isatuximab to red cells.**
- Imaging as per NICE/network guidance and clinical presentation

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Additional Investigations

1. Plasma viscosity if hyperviscosity suspected
2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
3. Counselling about risks in pregnancy - There are no available data on isatuximab use in pregnant women. Animal reproduction toxicity studies have not been conducted with isatuximab. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of isatuximab in pregnant women is not recommended.. Women of childbearing potential treated with isatuximab should use effective contraception during treatment and for at least 5 months after cessation of treatment. Patients must also comply with pregnancy prevention programme for pomalidomide.
4. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
5. Fertility - all patients should be offered fertility advice, as appropriate.
6. Hydration - fluid intake of at least 3 litres /day should be attempted.
7. Document patient's height and weight, dose on actual body weight.
8. Document patient's performance status.
9. Treatment must be agreed at the relevant MDT.

REGIMENSPECIFIC PRE-ASSESSMENT

1. Ensure patients are given a Patient ID Card for isatuximab and are instructed to carry this for 6 months after stopping treatment.
2. Advise patients to inform their other HCPs that they have received isatuximab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.
3. Obtain written consent for the treatment including signing Pregnancy Prevention Programme forms, relating to pomalidomide.

DRUG REGIMEN:

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Cycle 1	Pre-meds	Paracetamol 1g PO, Chlorphenamine 10 mg IV, Omeprazole 20mg PO Dexamethasone, see below montelukast 10 mg PO	To be given 30 minutes prior to isatuximab infusion
	Isatuximab	10mg/kg Intravenous infusion	Days 1, 8, 15 and 22
	Dexamethasone	40mg if <75 years, OR 20mg if ≥75 years	Days 1,8,15,22
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
Cycle 2 onwards	Pre-meds	Paracetamol 1g PO, Chlorphenamine 10 mg IV, Omeprazole 20mg PODexamethasone, see below	To be given 30 minutes prior to isatuximab infusion
	Isatuximab	10mg/kg Intravenous infusion	Days 1 and 15
	Dexamethasone	40mg if <75 years, OR 20mg if ≥75 years	Days 1,8,15,22
	Pomalidomide	4mg PO daily on days 1-21	NOCTE

Additional Post-medications: the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators), should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

INFUSION RATES

Isatuximab infusion should be administered intravenously at the infusion rate presented in the Table below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions

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	Dilution volume	Initial rate	Absence of infusion reaction	Rate increment	Maximum rate
First infusion	250 mL	25 mL/ hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/ hour
Second infusion	250 mL	50 mL/ hour	For 30 minutes	50 mL/ hour for 30 minutes then increase by 100 mL/ hr every 30 minutes	200 mL/ hour
Subsequent infusions	250 mL	200 mL/ hour	-----	-----	200 mL/ hour

For more information on infusion reactions, see section “**Infusion reactions**”. For management of infusion reactions, see section “**Managing infusion reactions**”

CYCLE FREQUENCY

The cycle is repeated every 28 days until disease progression.

DOSE MODIFICATIONS

Haematological

Isatuximab:

In the event of grade 4 neutropenia, isatuximab administration should be delayed until neutrophil count improves to at least $1.0 \times 10^9/L$. The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines.

Pomalidomide:

To initiate a new cycle of Pomalidomide, ANC $\geq 1.0 \times 10^9/L$ and Platelets $\geq 50 \times 10^9/L$

Toxicity	Dose Modification
Neutropenia:	
ANC $< 0.5 \times 10^9/L$ OR Febrile Neutropenia and ANC $< 1.0 \times 10^9/L$. When ANC return to $\geq 1 \times 10^9/l$	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at the next lower dose (e.g. if starting dose was 4mg, reduce to at 3 mg OD)
For each subsequent drop ANC $< 0.5 \times 10^9/L$ When ANC $\geq 1.0 \times 10^9/L$	Interrupt Pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose.

Thrombocytopenia:	
Platelets < 25 x 10 ⁹ /L	Interrupt Pomalidomide, monitor FBC weekly
When Platelets ≥ 50 x 10 ⁹ /L	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop Platelets < 25 x 10 ⁹ /L	Interrupt Pomalidomide
When Platelets ≥ 50 x 10 ⁹ /L	Resume pomalidomide treatment at one dose level lower than the previous dose.

If toxicities occur after dose reductions to 1 mg, then discontinue Pomalidomide.

Weekly injections of G-CSF can be administered to keep maintain dose intensity (aim to keep neutrophil counts >1.0)

Pomalidomide dosing levels:

Dose level	Oral pomalidomide dose
Starting dose	4mg
Dose level -1	3mg
Dose level -2	2mg
Dose level -3	1mg

Non-Haematological

Isatuximab:

For the management of infusion-related reactions, please see section below “Managing Infusion-related reactions”.

Pomalidomide

Toxicity	Dose Modification
-Grade 3 or 4 -When resolved to Grade ≤ 2	-Interrupt pomalidomide - Resume pomalidomide treatment at one dose level lower than the previous dose.
-Skin rash G2 or G3	-Interrupt or discontinue pomalidomide
-Skin rash G4 (exfoliative/bullous rash)	-Discontinue pomalidomide
Angioedema (all grades)	Discontinue pomalidomide

Renal and Hepatic Impairment

Isatuximab

Renal	Hepatic
Based on population pharmacokinetic analysis and on clinical safety, no dose adjustment is recommended in patients with mild to severe renal impairment	Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment. Data in patients with moderate and severe hepatic impairment are limited, but there is no evidence to suggest that dose adjustment is required in these patients.

Pomalidomide

Renal	Hepatic
No dose adjustment required in renal impairment On haemodialysis days, patients should take pomalidomide following haemodialysis	<p>Patients with serum total bilirubin > 1.5 x ULN were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide.</p> <p>No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.</p>

INVESTIGATIONS – during treatment

- FBC, U&Es, LFTs, Ca⁺⁺, glucose – every 4 weeks.
- Ig's, paraprotein, Freelite assay usually monthly
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and for 3 months afterwards.
- Prophylactic fluconazole 50mg OD.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-3)
- Proton pump inhibitor or H2 antagonist at clinician's discretion on days of steroids
- Thromboprophylaxis/anticoagulation see VTE section below.

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- Bone protection as per NSSG Bone Protection protocol MM.

EMETIC RISK

Low risk

EXTRAVASATION RISK

Unknown

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Isatuximab:

- **Interference with Serological Testing**

Because CD38 protein is expressed on the surface of red blood cells (RBCs), isatuximab, an antiCD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with isatuximab..

- I. **Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received isatuximab.**
- II. **Patients must be typed and screened prior to starting isatuximab.**
- III. Ensure patients are given a Patient ID Card for isatuximab and are instructed to carry this for 6 months after stopping treatment.
- IV. Ask patients to tell their other HCPs that they have received isatuximab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.

- **Interference with Determination of Complete Response**

Isatuximab is a human IgG kappa monoclonal antibody detectable on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

- **Testing for hepatitis B virus:**

All patients starting on isatuximab must be screened for hepatitis B virus before initiation,; patients with unknown serology who are already on treatment should also be screened

Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment, and for at least 6 months following the end of

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treatment.

Patients with positive serology need to be advised to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation

Treatment with isatuximab should be stopped in patients with hepatitis B virus reactivation; appropriate treatment needs to be instituted in consultation with experts in the treatment of hepatitis B virus infection; consult with experts before resuming isatuximab in patients with adequately controlled viral reactivation

Suspected adverse drug reactions associated with isatuximab need to be reported to the Yellow Card Scheme

- **Contraception**

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 5 months after cessation of isatuximab treatment.

Patient must comply with pregnancy prevention programme in order to be eligible to receive pomalidomide.

- **Infusion reactions**

Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA (see section 4.8). All infusion reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of an infusion reaction included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension and dyspnoea.

To decrease the risk and severity of infusion reactions, patients should be pre-medicated prior to isatuximab infusion with acetaminophen, H2 antagonists or proton pump inhibitors, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment. Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt isatuximab infusion and provide appropriate medical and supportive measures. In case symptoms do not improve after interruption of isatuximab infusion, recur after initial improvement with appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue isatuximab and institute appropriate management.

- **Managing Infusion related reactions**

Administration adjustments should be made if patients experience infusion reactions:

- In patients who experience Grade 2 (moderate) infusion reactions, a temporary interruption in the infusion should be considered and additional symptomatic medicinal products can be administered. After improvement to grade ≤ 1 (mild), infusion may be

resumed at half of the initial infusion rate under close monitoring and supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2.

- If symptoms do not resolve rapidly or do not improve to Grade ≤ 1 after interruption of the infusion, recur after initial improvement with appropriate medicinal products, or require hospitalization or are life-threatening (Grade ≥ 3), treatment with isatuximab should be permanently discontinued and additional supportive therapy should be administered, as needed.

- **Other common adverse effects:** Upper respiratory tract infections, pneumonia, bronchitis, febrile neutropenia, dyspnoea, diarrhoea, nausea, vomiting.

Pomalidomide:

- Venous thromboembolism (VTE): There is an increased risk of thrombosis with pomalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

1. Prophylactic low-molecular weight heparin OR
2. Prophylactic DOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for patients with additional risk factors.

If VTE occurs, pomalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- Fatigue, dizziness and confusion
- Peripheral neuropathy, diarrhea/constipation, pneumonia, peripheral oedema.
- Risks of cardiac failure, interstitial lung disease and hepatotoxicity: There is a published MHRA drug alert (2015) on pomalidomide and risks of cardiac failure, interstitial lung disease and hepatotoxicity. See weblink: <https://www.gov.uk/drug-safety-update/pomalidomide-immunoid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity>.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Michel Attal*, Paul G Richardson*, S Vincent Rajkumar, Jesus San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, Meletios A Dimopoulos, Jeffrey Shang-Yi Huang, Jiri Minarik, Michele Cavo, H Miles Prince, Sandrine Macé,

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2. Early access to medicines scheme (EAMS) scientific opinion: Isatuximab in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma. MHRA (2019). Available at: <https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-isatuximab-in-combination-with-pomalidomide-and-dexamethasone-for-adult-patients>
3. Imnovid® (Pomalidomide), eMC UK Summary of Product Characteristics, 02 May 2019
4. SARCLISA 20mg/mL. eMC UK Summary of Product Characteristics: June 2020 NICE CDF approval for IsaPomDex: <https://www.nice.org.uk/guidance/gid-ta10448/documents/final-appraisal-determination-document>

REVIEW

Name	Revision	Date	Version	Review date
Faouzi Djebbari (Haematology Pharmacist)	New protocol	January 2020	1.0	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Pre-meds updated	Feb 2020	1.1	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Pre-med section updated, need for bluteq updated	June 2020	1.2	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	1.3	June 2021
NSSG Myeloma Group	Minor update to infusion table	February 2021	1.4	June 2021
NSSG Myeloma Group	Minor update of pomalidomide dose reduction levels	May 2021	1.5	June 2021
Quality Manager	Nursing care plan added	May 2021	1.5	June 2021

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Nursing Care Plan: ISATUXIMAB WITH POMALIDOMIDE AND DEXAMETHASONE

Indication: Relapsed/refractory Myeloma.

Frequency: The cycle is repeated every 28 days until disease progression.

Alopecia: No

On cycle 1 day 1 send phenotyping bloods to the Transfusion Lab prior to Isatuximab infusion – send 3x EDTA tubes, all labelled with Safe Tx in a cross match sample bag, marked for the attention of a BMS 7. These bloods can be signed for on Aria once the sample has been sent. Please call the transfusion lab to let them know that phenotyping bloods are being sent because the patient is going to commence Isatuximab. Patient will require red cell phenotyping as cross match fails due to binding of Isatuximab to red cells.

ISATUXIMAB: Monoclonal antibody

Administered as an IV infusion in incremented rates.

Cycle 1 - days 1, 8, 15 and 22

Cycle 2 onwards - days 1 and 15

Isatuximab infusion should be administered at the infusion rate detailed on Aria – please note that there is an initial infusion rate and a subsequent rate. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions

Classification of extravasation: Unknown

Emetic risk: Low

Side effects: Interference with serological testing (for bloods transfusion), upper respiratory tract infections, pneumonia, bronchitis, febrile neutropenia, dyspnoea, diarrhoea, nausea, vomiting.

Dosing reactions: include dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension and dyspnoea. If a patient experiences a reaction, the infusion rate can be recommenced at half the previous rate when they are stable enough to recommence infusion, this must be done under close supervision.

POMALIDOMIDE: Immunomodulator and angiogenesis inhibitor.

Administered orally at night on **days 1-21**

Emetic risk: Low

Side effects: VTE, fatigue, dizziness and confusion, peripheral neuropathy, diarrhoea/constipation, pneumonia, peripheral oedema. Risks of cardiac failure, interstitial lung disease and hepatotoxicity.

DEXAMETHASONE: corticosteroid

Administered orally on **days 1, 8, 15 and 22** taken with or after food preferably at breakfast

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Pre-medications (as per protocol/Aria prescription) 30 minutes before commencing Isatuximab infusion.
- Ensure patients have been given a Patient ID Card for Isatuximab and are instructed to carry this for 6 months after stopping treatment, please check with Myeloma CNS team.
- Bloods are required at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.
- Advise patients to maintain fluid intake of 2-3 litres a day and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.

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