# Isatuximab plus pomalidomide and low dose dexamethasone (IsaPd)

## Indication

Treatment of adult patients with relapsed and refractory multiple myeloma only if they have received 3 previous lines of therapies (that included lenalidomide and a proteasome inhibitor) and have demonstrated disease progression on the last therapy.

NICE TA658

## ICD-10

Codes with a pre-fix C90.

## Regimen details

**Cycle 1**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1, 8, 15 and 22 | Isatuximab | 10mg/kg | IV infusion |
| 1-21 | Pomalidomide | 4mg OD | PO |
| 1, 8, 15 and 22 | Dexamethasone | 40mg OM* | PO |

* 20 mg OM for patients aged ≥ 75 years

**Cycle 2 onwards**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 and 15 | Isatuximab | 10mg/kg | IV infusion |
| 1-21 | Pomalidomide | 4mg OD | PO |
| 1, 8, 15 and 22 | Dexamethasone | 40mg OM* | PO |

* 20 mg OM for patients aged ≥ 75 years

## Cycle frequency

28 days

## Number of cycles

Continue until disease progression (e.g. International Myeloma Working Group (IMWG) criteria) or unacceptable toxicity.

## Administration

Isatuximab is an anti-CD38 IgG1 monoclonal antibody supplied as a 20mg/mL concentrate for solution for infusion, produced from the CHO cell line.

The first and subsequent doses of isatuximab should be given in an environment with resuscitation facilities. Isatuximab should be given after premedication. Isatuximab should be administered in sodium chloride 0.9% 250mL via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate (as per table below). Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

| | Volume of sodium chloride 0.9% | Initial infusion rate (first hour) | *Absence of infusion reaction | Rate increment | Maximum rate |
|---|---|---|---|---|---|
| First infusion | 250mL | 25mL/hour | For 60 minutes | 25mL/hour every 30 minutes | 150mL/hour |
| Second infusion | 250mL | 50mL/hour | For 30 minutes | 50 mL/hour for 30 minutes then increase by 100 mL/ hr | 200mL/hour |
| Subsequent infusions | 250mL | 200mL/hour | - | - | 200mL/hour |

*Infusion reactions – see adverse events.

Pomalidomide is available as 1mg, 2mg, 3mg and 4 mg capsules. Pomalidomide should be swallowed whole with water, either with or without food, at the same time each day. The capsules should not be broken, opened or chewed. Patients should be advised to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.
Pomalidomide must be prescribed and dispensed in accordance with the Pregnancy Prevention Programme. Prescription authorisation is required for each dispensing (see additional information below).

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken 15-60 minutes prior to isatuximab infusion, with or after food.

## Pre-medication

15-60 minutes prior to isatuximab infusion:
Paracetamol 500mg-1g PO,
Chlorphenamine 10 mg IV; after the first 4 infusions may be switched to 4mg PO if no infusion related reactions.
Dexamethasone 40mg PO (20mg for ≥ 75 years of age). This is included in the total dose of dexamethasone to be administered as part of the treatment.

Montelukast 10mg PO >30 mins prior to first infusion only.

Patients who do not experience an infusion reaction during their first 4 infusions of Isatuximab can have requirement for premedication with subsequent cycles reconsidered.

## Post infusion medication

For patients with a history of obstructive pulmonary disorder, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major infusion related reactions, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

## Emetogenicity

This regimen has low emetogenic potential.

## Additional supportive medication

Unless contraindicated, VTE thromboprophylaxis is required. Aspirin is appropriate for patients who have no additional risk factors. For patients with additional thromboembolic risk factors (such as immobility, dexamethasone >20mg/day) a low molecular weight heparin is recommended for the first 4 cycles. It may then be appropriate to switch to aspirin.
$H_2$ antagonist or proton pump inhibitor, ensure patients have taken on days of isatuximab treatment
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only
Bisphosphonates as per local policy.
Antifungal, antiviral and PCP prophylaxis as per local policy.

## Extravasation

Isatuximab – neutral (Group 1)

## Investigations – pre cycle 1

| Investigation | Validity period |
|---|---|
| FBC | Baseline – results valid for 7 days |
| U+Es (including creatinine) | Baseline – results valid for 7 days |
| LFTs | Baseline – results valid for 7 days |
| Group and Save<br>Request blood group and extended phenotype | Inform transfusion laboratory that patient is due to commence isatuximab. |
| Urine pregnancy test<br>(women of childbearing potential) | 3 days<br>Prescription dispensed within 7 days of the pregnancy test* |
| Viral screening – HIV, hepatitis B and C | - |
| Consider baseline cardiac and respiratory assessment | See MHRA alert below |

*Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day

**Pomalidomide is contraindicated in women of childbearing potential, unless all the conditions of the pregnancy prevention programme are met and in men unable to follow or comply with the required contraceptive measures.**

**Other recommended tests for staging, informing treatment and assessing response:**
Calcium
Albumin
Uric acid
CRP
Glucose
Plasma viscosity
Serum protein electrophoresis and immunofixation for quantitation of monoclonal protein and immunoglobulins
Serum free light chain assay
β2 microglobulin
LDH
Marrow myeloma FISH.

**Nb. Isatuximab is an IgG kappa monoclonal antibody detectable on both serum protein electrophoresis and immunofixation. It may interfere with the determination of complete response and of disease progression**.

## Investigations – pre subsequent cycles

| Investigation | Validity period |
|---|---|
| FBC | 72 hours |
| U+Es (including creatinine) | 72 hours |
| LFTs | 72 hours |
| Glucose | - |
| Pregnancy test<br>(women of child bearing potential) | 3 days<br>Prescription dispensed within 7 days of the pregnancy test |

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

| Investigation | Limit |
|---|---|
| Neutrophils* | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 50 x $10^9$/L |
| Creatinine clearance | ≥ 30mL/min |
| Bilirubin | < 1.5 x ULN |
| ALT | < 3 x ULN |

*Consider the use of G-CSF to maintain dose intensity.

## Dose modifications

- **Haematological toxicity**

**Isatuximab:**

In the event of Grade 4 neutropenia (<0.5 x $10^9$/L), isatuximab administration should be delayed until neutrophil count improves to at least 1.0 x$10^9$/L. The use of colony-stimulating factors (e.g. G-CSF) should be considered.

**Pomalidomide:**

Prior to commencing a new cycle: neutrophils ≥ 1.0 x $10^9$/L and platelets ≥ 50 x $10^9$/L

**Thrombocytopenia**

Platelets should be ≥ 50 x $10^9$/L to commence a new cycle of treatment. If platelets drop to < 25 x $10^9$/L during the cycle pomalidomide treatment should be interrupted and FBC checked weekly. Pomalidomide can restart at the next dose reduction level once platelets have recovered to ≥ 50 x $10^9$/L as outlined below.

| Dose level | Oral Pomalidomide Dose |
|---|---|
| Starting dose | 4mg OD |
| Dose level -1 | 3mg OD |
| Dose level -2 | 2mg OD |
| Dose level -3 | 1mg OD |

**Neutropenia**

| **Neutrophils** (x $10^9$/L) | **Action** |
|---|---|
| <0.5 or febrile neutropenia (neutrophils <1.0 x $10^9$/L + fever)<br>(1st occurrence) | Withhold pomalidomide, monitor FBC weekly<br>Once recovered to ≥ 1.0 x $10^9$/L resume at 3mg OD |
| < 0.5 or febrile neutropenia<br>(2nd occurrence) | Withhold pomalidomide, monitor FBC weekly<br>Once recovered to ≥ 1.0 x $10^9$/L resume at 2mg OD |
| < 0.5 or febrile neutropenia<br>(3rd occurrence) | Withhold pomalidomide, monitor FBC weekly<br>Once recovered to ≥ 1.0 x $10^9$/L resume at 1mg OD |

If toxicities persist after dose reduction to 1mg, then discontinue pomalidomide.

Consider use of G-CSF to maintain dose intensity.

- **Renal impairment**

**Isatuximab:** No dose adjustment is recommended

**Pomalidomide:** No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take pomalidomide following haemodialysis.

- **Hepatic impairment**

**Isatuximab:**

| Bilirubin | | ALT | Recommendation |
|---|---|---|---|
| <1.5 x ULN | and | < 3 x ULN | No dose adjustment required |
| ≥1.5 xULN | or | ≥ 3 x ULN | Limited data but suggests no dose adjustment required. Discuss with consultant. |

**Pomalidomide:** 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. No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.

- **Other toxicities**

**Pomalidomide:**
**MHRA alert - Cardiac failure/interstitial lung disease/ hepatotoxicity:**
- Use with caution in cardiac disease or those with cardiac risk factors. Monitor for signs and symptoms of cardiac failure.
- If patient reports acute or worsening respiratory symptoms, stop pomalidomide and assess promptly to exclude/confirm interstitial lung disease. If confirmed, assess risks and benefits of restarting treatment.
- Liver function must be regularly monitored, particularly during the first 6 months of treatment.
**https://www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity**

For any Grade 3 or 4 toxicities, stop treatment and restart treatment with a 1 mg dose reduction, when resolved to ≤ Grade 2 at the physician's discretion.

If adverse reactions occur after dose reductions to 1 mg, discontinue pomalidomide. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, and should not be resumed following discontinuation for these reactions.

**Steroid side effects:**

If necessary, dexamethasone dosing should be modified using the following dosing levels:

| **Age < 75 years** | | **Dexamethasone dose** |
|---|---|---|
| | Starting dose | 40mg OM on days 1, 8, 15 and 22 |
| | Dose level -1 | 20mg OM on days 1, 8, 15 and 22 |
| | Dose level -2 | 10mg OM on days 1, 8, 15 and 22 |
| **Age ≥ 75 years** | | |
| | Starting dose | 20mg OM on days 1, 8, 15 and 22 |
| | Dose level -1 | 12mg OM on days 1, 8, 15 and 22 |
| | Dose level -2 | 8mg OM on days 1, 8, 15 and 22 |

**Dexamethasone dose modifications**

| Toxicity | Grade | Dose Modification |
|---|---|---|
| Dyspepsia | Grade 1-3 | Maintain dose and treat with $H_2$ antagonist or equivalent.<br>Reduce dose one level if symptoms persist. |
| | ≥ Grade 3 | Withhold until symptoms are controlled.<br>Add $H_2$ antagonist or equivalent and resume with one dose level reduction. |
| Oedema | ≥ Grade 3 | Use diuretics as needed and continue with one dose level reduction. |
| Confusion or mood alteration | ≥ Grade 2 | Withhold until symptoms resolve.<br>Resume with one dose level reduction. |
| Muscle weakness | ≥ Grade 2 | Withhold until muscle weakness ≤ Grade 1.<br>Resume with one dose level reduction. |
| Hyperglycaemia | ≥ Grade 3 | Reduce dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed. |
| Acute pancreatitis | | Discontinue dexamethasone. |
| Other dexamethasone adverse events | ≥ Grade 3 | Withhold until resolved to ≤ Grade 2.<br>Resume with one dose level reduction. |

If recovery from dexamethasone toxicity is prolonged beyond 14 days, the dose should be reduced by one dose level.

## Adverse effects - for full details consult product literature/ reference texts

**Isatuximab Infusion reactions**

Infusion reactions, mostly mild or moderate, were observed in 38.2% of patients treated with isatuximab. Almost all infusion reactions started during the first infusion and resolved on the same day. 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 (see above). Vital signs should be frequently monitored during the entire infusion and if required interrupt the infusion and provide appropriate medical and supportive measures. 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), the isatuximab infusion may be resumed at half of the initial infusion rate under close monitoring. 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 the infusion table in the administration section above. If infusion reactions do not resolve or, recur after initial improvement with appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue isatuximab and institute appropriate management.

**Teratogenicity**

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening birth defects and pomalidomide is teratogenic in animal studies.

Adverse reactions tend to occur more frequently within the first 2 cycles of treatment with pomalidomide.

- **Serious side effects**

Pneumonia
Myelosuppression
Tumour lysis syndrome
Haemorrhage
Thromboembolic events
Peripheral neuropathy

Cardiotoxicity
Interstitial lung disease
Second primary malignancy – see SPC
Treatment Related Mortality estimated < 5%

- **Frequently occurring side effects**

Isatuximab infusion-related reactions – see SPC for management
Myelosuppression
Respiratory tract infection
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Peripheral neuropathy
Peripheral oedema
Sleep disturbance, psychosis (dexamethasone)
Hepatic dysfunction

- **Other side effects**

Dizziness
Confusion

## Significant drug interactions – for full details consult product literature/ reference texts

If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions due to P450 isoenzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters.

## Additional comments

In line with the conditions of the Pregnancy Prevention Programme - dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks, and prescriptions for all other patients can be for a maximum duration of 12 weeks.

**Interference with Blood Transfusion Serological Testing**
See Isatuximab SPC for full details.

**Interference with determination of monoclonal protein concentration**
See Isatuximab SPC for full details.

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## References


- Summary of Product Characteristics: Pomalidomide (Celgene) accessed 24 Nov 2020 via www.medicines.org.uk
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- Attal M et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *The Lancet* 2019; 394: 2045-2047.

- MHRA drug alert (2015) Accessed 27 July 2016 via www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity
- EAMS for IPd accessed 30 Dec 2019 via https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-isatuximab-in-combination-with-pomalidomide-and-dexamethasone-for-adult-patients
- Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [TA658] https://www.nice.org.uk/guidance/TA658


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