Indication	4th line treatment for relapsed and/or refractory multiple myeloma. Patients must have had 3 and only 3 previous lines of therapy that have included at least 2 consecutive cycles of lenalidomide (alone or in combination) and at least 2 consecutive cycles of a proteasome inhibitor eg bortezomib or carfilzomib or ixazomib (alone or in combination) and have shown disease progression on the last therapy. Patients must not have had any prior treatment with pomalidomide. Patients must have either not had previous therapy with any anti-CD38 antibody (eg daratumumab) or if there has been previous treatment with an anti-CD38 antibody, then the patient has received isatuximab via the EAMS scheme or the Sanofi early access scheme or did not progress whilst still receiving an anti-CD38 therapy other than isatuximab or did not progress within 60 days of the last infusion of an anti-CD38 treatment other than isatuximab. The use of isatuximab in combination with pomalidomide and dexamethasone in the 1-prior, 2-prior, 4-prior and >4-prior patient groups is not permitted within the CDF. A formal medical review must occur by the end of the first 8 weeks of treatment to determine whether treatment with isatuximab should continue or not.
Treatment Intent	Palliative-aiming to delay tumour progression.
Frequency and number of cycles	Repeat every 28 days. Until disease progression or excessive toxicity or patient choice to discontinue.
Monitoring Parameters pre-treatment	• Check virology status prior to cycle 1. • Monitor FBC at baseline, then weekly for the first 8 weeks and then at each cycle thereafter. • U&Es and LFTs at each cycle. • Baseline haematological parameters: CrCl>30ml/min, platelets >75x10^9/l and neutrophils >1 x 10^9/l. Bilirubin </=2 x ULN and AST and/or ALT </= 3 x ULN • Continuing haematological parameters: CrCl>30ml/min, platelets >50x10^9/l and neutrophils >1 x 10^9/l. • Haematological parameters requiring dose modification: Neutropenia, in the event of grade 4 neutropenia (neuts <0.5), isatuximab administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/l. Consider the use of colony-stimulating factors (e.g. G-CSF) in line with local guidelines. • BP at each cycle. • Blood glucose every cycle. • Cases of hyperthyroidism have been report with pomalidomide, baseline and ongoing monitoring of thyroid function is recommended. • **Renal impairment:** • Isatuximab: No dose adjustment required. • Pomalidomide: No dose adjustment required. • **Hepatic impairment:** • Isatuximab: No dose adjustment required in mild hepatic impairment. Limited data in moderate or severe impairment, clinical decision. • Pomalidomide: No recommended dose adjustment. Increased monitoring required in hepatic impairment and dose reduction or interruption may be required due to adverse reactions. • **Interference with tests:** Isatuximab binds to CD38 on red blood cells and may result in a positive Indirect Antiglobulin Test (Coombs test) which may persist for up to 6 months after the last infusion. Send a blood sample for group/ direct

antiglobulin/phenotype testing prior to treatment. Isatuximab may be detected on SPE and IFE assays resulting in false positive results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses.

- **Dose modification:**
- Isatuximab: no dose reduction recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity.
- Pomalidomide: see table 1 and 2 below.
- Dexamethasone: *Dose reduction to 20mg in patients who are ≥75 years.
- **Drug Interactions:**
  If strong inhibitors of CYP1A2 (e.g. ciprofloxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.
- **Isatuximab infusion rate and infusion related reactions (IRRs):**
  Isatuximab can cause severe infusion reactions. Pre-meds must be given 15-60 minutes before the infusion and patients must be monitored during the entire infusion. For patients that experience any Grade IRRs, continue monitoring post-infusion until symptoms resolve.
- **Patients who do not experience an infusion reaction upon their first 4 administrations of isatuximab may have their need for subsequent premedication reconsidered.
- **Infusion rate of first infusion (diluted in 250ml):** Administer at 25ml/hr for the first hour. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 25ml/hr every 30 minutes to a maximum rate of 150ml/hr.
- **Infusion rate of second infusion (diluted in 250ml):**
  Second infusion: Administer at 50ml/hr for 30 minutes. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated by 50ml/hr for 30 minutes then increase by 100ml/hr every 30 minutes to a maximum rate of 200ml/hr.
- **Subsequent infusions:** Administer at 200ml/hr.
  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), isatuximab 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 described above) in increments of 100 mg/hr every 30 minutes to a maximum rate of 400mg/hr.
  If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of isatuximab 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.
- **Adverse reactions:**
- **Thromboembolic events:**
  Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored and VTE prophylaxis considered. Patients should be instructed to report any new symptoms such as shortness of breath, chest pain, arm or leg swelling.
- **Tumour Lysis Syndrome: (TLS)**
  Monitor for signs and symptoms of TLS. Appropriate measures (hydration, allopurinol, rasburicase) must be taken to prevent hyperuricemia as clinically indicated.

	• **Severe Cutaneous Adverse Reactions (SCARs)** Pomalidomide can induce severe skin reactions such as Stevens-Johnson syndrome. Patients should be informed of the possibility of severe skin reactions such as Stevens-Johnson syndrome and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur. • **Interstitial lung disease (ILD)** Patients should report any new respiratory symptoms. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks. • **Progressive multifocal leukoencephalopathy (PML)** PML has been reported in patients receiving pomalidomide. Patients should be monitored for new or worsening neurological, cognitive or behavioural changes. All treatment should be held if PML is suspected and permanently discontinued if PML is confirmed. • **Missed dose:** • If a planned dose of isatuximab is missed, the dose should be administered as soon as possible and the treatment schedule adjusted to maintain the treatment interval. • Ensure Pomalidomide pregnancy prevention programme forms are completed with each prescription. The PAF must be submitted to Celgene for every dispensing event. • **Contraception:** To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 5 months after cessation of isatuximab treatment. • **Driving**: Dizziness and fatigue are reported side effects; patients should review their ability to drive dependant on symptoms.
References	KMCC protocol HEAM-MYEL-039 v1 SPC pomalidomide accessed online 19.10.20 BNF accessed online19.10.20 Blueteq form accessed online 19.10.20 SPC isatuximab accessed online 19.10.20

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Pomalidomide dose modification instructions

Toxicity	Dose modification
Neutropenia ● ANC●● < 0.5 x 10^9/l or febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/l)	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC●●● weekly.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 0.5 x 10^9/l	Interrupt pomalidomide treatment.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia Platelet count < 25 x 10^9/l	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC●●● weekly.
Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 25 x 10^9/l	Interrupt pomalidomide treatment.
Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Rash Rash = Grade 2-3	Consider dose interruption or discontinuation of pomalidomide treatment.
Rash = Grade 4 or blistering (including angioedema, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected)	Permanently discontinue treatment (see section 4.4).
Other Other ≥ Grade 3 pomalidomide-related adverse events	Interrupt pomalidomide treatment for remainder of cycle. Resume at one dose level lower than previous dose at next cycle (adverse event must be resolved or improved to ≤ Grade 2 before restarting dosing).

●In case of neutropenia, the physician should consider the use of growth factors.
●●ANC – Absolute Neutrophil Count; ●●●CBC – Complete Blood Count.

Table 2 Pomalidomide dose reduction

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

Cycle 1 only: 28 day cycle.

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1, 8, 15 and 22	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion.
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	Stat Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).	
	Dexamethasone	40mg (*20 mg oral/IV for patients ≥75 years of age)	PO/IV	stat	
	ISATUXIMAB	**10mg/kg**	IV	**See notes above**	Dilute in 250ml 0.9% sodium chloride. Administer with in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter.
TTO	Drug	Dose	Route	Directions	
	POMALIDOMIDE	**4mg**	PO	OD on day's 1-21 only. Swallow whole with a whole glass of water. Do not crush or open the capsules. Complete prescription authorisation form. Capsules available in 1mg, 2mg 3mg and 4mg.	
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, then prescribe as required.	
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required Do not take for more than 5 days continuously.	
	Aciclovir	400mg	PO	TWICE daily.	
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays.	
	Omeprazole	20mg	PO	Daily. On Isatuximab treatment days take 15-60minutes prior to infusion.	
	Allopurinol	300mg	PO	OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.	
	Consider anti-fungals and prophylactic anticoagulation				

Cycle 2 onwards: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1 and Day 15	Chlorphenamine	10mg Chlorphenamine 4mg PO may be given as an alternative to IV from 5th administration onwards	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. (**see notes above)
	Paracetamol	1000mg	PO	stat	
	Omeprazole*	20mg	PO	Stat Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).	
	Dexamethasone	40mg (*20 mg oral/IV for patients ≥75 years of age)	PO/IV	stat	
	ISATUXIMAB	**10mg/kg**	IV	**See notes above**	Dilute in 250ml 0.9% sodium chloride. Administer with in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter.
TTO	Drug	Dose	Route	Directions	
	POMALIDOMIDE	**4mg**	PO	OD on days 1-21 only. Swallow whole with a whole glass of water. Do not crush or open the capsules. Complete prescription authorisation form. Capsules available in 1mg, 2mg 3mg and 4mg.	
	Dexamethasone	40mg	PO	OM on days 8 and 22 only. With or after food.	
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, then prescribe as required.	

	Metoclopramide	10mg	PO	Take 10mg up to TDS when required Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	TWICE daily.
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays.
	Omeprazole	20mg	PO	Daily. On Isatuximab treatment days take 15-60minutes prior to infusion.
	Consider anti-fungals and prophylactic anticoagulation			