Indication	Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of newly diagnosed UNTREATED multiple myeloma when a stem cell transplant is unsuitable. Patients may have commenced induction therapy with the combination of daratumumab plus bortezomib, thalidomide and dexamethasone with the intention of proceeding to a stem cell transplant but despite responding to such treatment the patient is now ineligible for transplantation. NB not funded for primary amyloidosis patients
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 28 days Continue until disease progression or excessive toxicity or patient choice to discontinue.

Monitoring Parameters pre-treatment	• **Lenalidomide Prescription Authorisation Form must be completed at time of prescribing.**
	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• Consider flu and pneumococcal vaccination pre-therapy.
	• Monitor **FBC** at baseline, then weekly for the first 8 cycles and then at each cycle thereafter.
	• **U&Es** and **LFTs** at each cycle.
	• Baseline haematological parameters: platelets >75x10^9/l and neutrophils >1 x 10^9/l.
	• Continuing haematological parameters: platelets >50x10^9/l and neutrophils >1 x 10^9/l.
	• **BP** baseline and if clinically indicated thereafter.
	• **Lung function** assessment required in patients with pre-existing respiratory disease (COPD, asthma) and heavy smokers. Clinician to decide if further imaging required in patients with additional co-morbidities.
	• **Hepatic impairment:**
	  ○ **Isatuximab:** No dose adjustment required in mild hepatic impairment. Limited data in moderate or severe impairment, clinical decision.
	  ○ **Bortezomib:** Consider dose reduction in moderate/severe hepatic impairment (Bilirubin >1.5ULN), reduce Bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
	  ○ **Lenalidomide:** no specific dose recommendations.
	• **Renal impairment:**
	  ○ **Isatuximab:** No dose adjustment required in patients with mild to severe renal impairment including end-stage renal disease.
	  ○ **Bortezomib:** CrCl < 20ml/min discuss with consultant.
	  ○ **Lenalidomide:** CrCl 30-49ml/min, give 10mg od (the dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment); CrCl <30ml/min, give 15mg on alternate days, days 1 to 21. End stage renal disease (CrCl <30ml/min requiring dialysis) give 5mg OD on days 1 to 21, administer after dialysis. NB an alternative dosing schedule which may be considered, but is not within the licence, is: CrCl 30-49ml/min, give 25mg on alternate days; CrCl <30ml/min, give 25mg twice a week.
	  ○ **Allopurinol:** Ensure renal function is normal before prescribing allopurinol (usual dose is 300mg od). Reduce Allopurinol dose to 100mg od if CrCl is 10-20ml/min. Reduce Allopurinol dose to 100mg on alternate days if CrCl is <10ml/min.
	• **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 at least 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.

- **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 with paracetamol and chlorphenamine 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):** 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 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).
  - 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.
- **Drug specific cautions and dose adjustments:**
- **Isatuximab:** no dose reduction recommended.
  Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. In the event of Grade 3 or 4 neutropenia withhold until improvement to grade 2 or better. Consider the use of colony-stimulating factors (e.g. G-CSF) in line with local guidelines.
- **Bortezomib cycle 1 to 8:**
  - ECG baseline and if clinically indicated thereafter.
  - Use with caution in patients with pre-existing heart disease or with high risk factors.
  - Patients should be advised to report any new or worsening respiratory symptoms.
  - At least 72 hours must elapse between consecutive Bortezomib doses.
  - Ensure patient is well hydrated (drinking ~3L/day) prior to treatment.
  - **Dose modification bortezomib:** If Hb < 65g/l transfuse patient and restart treatment when Hb >65g/l.
  - Bortezomib should be withheld for any grade 3 non-haematological (see below for guidance on managing neuropathic toxicities) or Grade 4 haematological toxicities (neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L); once toxicity has settled reinitiate at 75%, (i.e. 1.3mg/m^2 → 1.0mg/m^2 → 0.7mg/m^2).
  - For Neuropathic Pain and or Peripheral Sensory or Motor Neuropathy dose reductions see table 1.
- **Lenalidomide:**
  - **Haematological toxicity:** Treat when neutrophils >/= 1.0 x 10^9/L and platelets >/= 50 x 10^9/L. If neutrophils fall below 0.5 x 10^9/L interrupt treatment and resume at starting dose once resolved to >/=1 x 10^9/L if neutropenia is the only observed toxicity, if other dose dependant

	haematological toxicities are observed other than neutropenia resume at one reduced dose level when neutrophils have resolved to >/=0.5 x 10^9/L. For each subsequent episode of neutropenia (<0.5 x 10^9/L) interrupt treatment and decrease the dose of lenalidomide to the next dose level when neutrophils have returned to >/=0.5x10^9/L (see table 2). If platelets fall to <25 x 10^9/L interrupt treatment for the remainder of the cycle and resume at one reduced dose level once resolved to >/=50 x 10^9/L. ○ **Non-Haematological toxicity:** For other Grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to </= Grade 2 depending on the physician's discretion. ○ Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, 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, and should not be resumed following discontinuation from these reactions. ○ Treatment with lenalidomide has been associated with an increased risk of venous thromboembolism. All patients should be risk assessed and prophylactic anticoagulation prescribed as per standard of care. • **Dexamethasone:** Dose reduction may be considered in patients who are >75 years, patients who have a BMI <18.5, patients with poorly controlled diabetes mellitus or who have had prior intolerance/adverse event (AE) to steroid therapy. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • **Bortezomib:** ○ The concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced. CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) should be used with caution and patients monitored for toxicity. ○ Patients on oral hypoglycaemic agents require close monitoring of blood sugar levels. • **Lenalidomide:** ○ Monitoring of digoxin concentration is advised during lenalidomide treatment with concomitant use. ○ Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with Lenalidomide. Manufacturer advises avoid. • **Missed dose:** ○ **Lenalidomide:** If less than 12 hours after the usual administration time the patient should take the dose and continue as normal the following day. If more than 12 hours after the usual administration time the dose should be omitted and continue with the schedule the following day. ○ **Isatuximab:** If a dose of isatuximab is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval. • **Contraception and Pregnancy:** • Ensure patient is informed of requirement for strict contraception precautions during treatment with Lenalidomide. Follow Lenalidomide risk management programme. Pregnancy test every 4 weeks if patient is of child-bearing potential. • Male and female patients who are able to have children must use **effective contraceptive measures during treatment.** • Female patients should use effective contraception for 8 months after cessation of bortezomib treatment and for 5 months after cessation of isatuximab treatment. • Male patients should be advised not to father a child while receiving bortezomib and for 5 months following completion of treatment.

	• **Driving and Machinery:** Patients should be advised that lenalidomide and bortezomib can affect the ability to drive and use machines. If patients experience fatigue/dizziness or blurred vision they should not drive. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	SPC accessed online 26.09.2025 CDF list accessed online 26.09.2025 BlueTeq form accessed online 26.09.2025 ACN protocol "IsaVRd once weekly for 1L MM v1 Sep 2025"

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

Table 1: Dose modification of bortezomib for neuropathic toxicities

Severity of neuropathy	**Posology modification**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue bortezomib
*Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 **Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc; ***Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

Table 2: Dose reduction for lenalidomide:

	Lenalidomide
Starting dose	25 mg
Dose level -1	20 mg
Dose level -2	15 mg
Dose level -3	10 mg
Dose level -4	5 mg
Dose level -5	2.5 mg

Cycle 1 only: 28 day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1, 8, 15, 22	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	stat	
	Dexamethasone	20mg	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.
	BORTEZOMIB	**1.3mg/m^2**	SC	bolus	Inject in to the thigh or abdomen at a 45-90^o angle. Injection sites should be rotated from left to right.
TTO	Drug	Dose	Route	Directions	
Day 1	**DEXAMETHASONE**	**20mg**	PO	OM on days 2, 9, 16, and 23. Take with or after food.	
	LENALIDOMIDE	**25mg**	PO	OD on **days 1 to 21** followed by 7 days' rest. (available as 2.5mg, 5mg, 10mg, 15mg, 20mg and 25mg capsules)	
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)	
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)	
	Apixaban	2.5mg	PO	BD	
	Omeprazole	20mg	PO	OD	
	Allopurinol	300mg	PO	OD for 28 days then review.	
	Loperamide	2mg-4mg	PO	Take 4mg (TWO capsules) initially, then 2mg (ONE capsule) after each loose stool when required. Max. 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if prescribed.	
	Consider prophylactic antifungals				
	Consider levofloxacin prophylaxis for 12 weeks (cycles 1 to 3 only) for all newly diagnosed myeloma patients				

Cycle 2 to 8: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	stat	
	Dexamethasone	20mg	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.
	BORTEZOMIB	**1.3mg/m²**	SC	bolus	Inject in to the thigh or abdomen at a 45-90° angle. Injection sites should be rotated from left to right.
8	**BORTEZOMIB**	**1.3mg/m²**	SC	bolus	Inject in to the thigh or abdomen at a 45-90° angle. Injection sites should be rotated from left to right.
15	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	stat	
	Dexamethasone	20mg	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.
	BORTEZOMIB	**1.3mg/m²**	SC	bolus	Inject in to the thigh or abdomen at a 45-90° angle. Injection sites should be rotated from left to right.
22	**BORTEZOMIB**	**1.3mg/m²**	SC	bolus	Inject in to the thigh or abdomen at a 45-90° angle. Injection sites should be rotated from left to right.

Cycle 2 to 8 TTOs

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**20mg**	PO	OM on days 2, 8, 9, 16, 22 and 23. Take with or after food.
	LENALIDOMIDE	**25mg**	PO	OD on **days 1-21** followed by 7 days' rest. (available as 2.5mg, 5mg, 10mg, 15m, 20mg and 25mg capsules)
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Omeprazole	20mg	PO	OD
	Apixaban	2.5mg	PO	BD
	Loperamide	2mg-4mg	PO	Take 4mg (TWO capsules) initially, then 2mg (ONE capsule) after each loose stool when required. Max. 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if prescribed.
	Consider prophylactic antifungals			
	Consider levofloxacin prophylaxis for 12 weeks (cycles 1 to 3 only) for all newly diagnosed myeloma patients			

Cycle 9 to 17: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1 and 15	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	stat	
	Dexamethasone	20mg	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
Day 1	**DEXAMETHASONE**	**20mg**	PO	OM on days 2, 8, 9, 16, 22 and 23. Take with or after food.
	LENALIDOMIDE	**25mg**	PO	OD on **days 1-21** followed by 7 days' rest. (available as 2.5mg, 5mg, 10mg, 15mg, 20mg and 25mg capsules)
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Apixaban	2.5mg	PO	BD
	Omeprazole	20mg	PO	OD
	Loperamide	2mg-4mg	PO	Take 4mg (TWO capsules) initially, then 2mg (ONE capsule) after each loose stool when required. Max. 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if prescribed.
	Consider prophylactic antifungals			

Cycle 18 onwards: Repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Chlorphenamine	10mg	IV	Slow bolus over 1min	To be administered 15-60min before isatuximab infusion. Ensure patient has taken TTO omeprazole 15-60 mins before isatuximab (or use stock on day 1).
	Paracetamol	1000mg	PO	stat	
	Omeprazole	20mg	PO	stat	
	Dexamethasone	20mg	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
Day 1	**DEXAMETHASONE**	**20mg**	PO	OM on days 2, 8, 9, 15, 16, 22 and 23. Take with or after food.
	LENALIDOMIDE	**25mg**	PO	OD on **days 1-21** followed by 7 days' rest. (available as 2.5mg, 5mg, 10mg, 15mg capsules)
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Apixaban	2.5mg	PO	BD
	Omeprazole	20mg	PO	OD
	Loperamide	2mg-4mg	PO	Take 4mg (TWO capsules) initially, then 2mg (ONE capsule) after each loose stool when required. Max. 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if prescribed.
	Consider prophylactic antifungals			