Indication	For the treatment of newly diagnosed and treatment-naive multiple myeloma in patients who are ineligible for an autologous stem cell transplant. NB this is not funded for patients with primary amyloidosis.
Treatment Intent	Disease modification
Frequency and number of cycles	Every 28 days Cycle **1** and **2** every 28 days: weekly daratumumab (8 doses in total) Cycle **3** to **6** every 28 days: 2 weekly daratumumab (8 doses in total) Cycle **7** onwards 28 days: 4 weekly daratumumab Continue until progressive disease or unacceptable toxicity or patient choice, whichever occurs first. NB the first administration of daratumumab can be given in split doses on different days if IV infusion is used instead of subcutaneous daratumumab. A formal medical review **MUST** occur by the end of the first 8 weeks of treatment to establish whether treatment should continue.
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. • If positive hepatitis B viral serology is found, the patient should be monitored for hepatitis B virus reactivation. • Consider flu and pneumococcal vaccination pre-therapy. • Monitor LFT's and U&Es on day 1 of each cycle. • FBC on day 1, 8 and 15 for the first 2 cycles and then on day 1 only of each cycle thereafter. • Lenalidomide treatment must not be started if the Absolute Neutrophil Count (ANC) is <1.0 x 10^9/L, and/or platelet counts are <50 x 10^9/L. • Thyroid function at baseline and as clinically indicated throughout treatment. • **Hepatic impairment:** o Daratumumab: no recommended dose adjustment. o Lenalidomide: Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations. • **Renal impairment:** o Daratumumab: No dose adjustments necessary. o Lenalidomide: No dose reduction required in mild impairment. If CrCl 30-49ml/min, give 10mg OD, after 2 cycles if the patient is tolerating this dose but not responding to treatment the dose may be escalated to 15mg OD. If CrCl <30ml/min give 15mg on alternate days. If CrCl <30ml/min requiring dialysis give 5mg OD, on dialysis days the dose should be given following dialysis. o Allopurinol: Ensure renal function is normal before prescribing Allopurinol (usual dose is 300 mg od). Reduce Allopurinol dose to 100mg od if CrCl is 10-20ml/min and 100mg on alternate days if CrCl is <10ml/min. • **Daratumumab injection related reactions (IRRs):** o Daratumumab can cause severe injection reactions which may result in admission to hospital. Pre-meds must be given 1-3 hours before the injection.

- Patients should be pre-medicated with chlorphenamine, dexamethasone and paracetamol as well as monitored (vital signs before and after the injection) and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. Daratumumab therapy should be discontinued immediately and permanently. Patients should be observed for 6 hours post the 1st injection, 2 hours after 2nd dose and then 15 minutes observation after subsequent doses.
- 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.

- **Administration of sub cut daratumumab:**
  - Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections.
  - Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, and hard or areas where there are scars.
  - Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
  - During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.
- **Drug specific cautions and dose adjustments:**
  - **Daratumumab:** Limited data of daratumumab SC in patients >120kg, give at clinicians' discretion.
  - Contraception: To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.
  - No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity.
  - **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 1).
    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.

	○ Ensure patient is informed of requirement for strict contraception precautions during treatment with Lenalidomide. Follow Lenalidomide risk management programme. ○ Pregnancy test – if patient is of child-bearing age (every 4 weeks). ○ Treatment with lenalidomide has been associated with an increased risk of venous thromboembolism. All patients should be risk assessed and prophylactic anticoagulation considered. ○ **Dexamethasone:** Dose reduction should 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. • **Interference with tests (refer to company risk materials):** Daratumumab binds to CD38 on red blood cells and results 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. Daratumumab 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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Daratumumab**: No interaction studies have been performed. ○ **Lenalidomide**: Lenalidomide may increase digoxin concentration, monitor digoxin levels during treatment. Increased risk of rhabdomyolysis when administered with statins. Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with Lenalidomide. Manufacturer advises avoid. • **Missed dose:** ○ **Daratumumab:** If a planned dose is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval. ○ **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. • **Driving:** Patients should be advised that lenalidomide can have an effect on their ability to drive and use machines. • **For oral self-administration:** refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	CDF V1.277 accessed online 17.10.2023 KMCC protocol HAEM-MYEL-040 V2 SPC daratumumab accessed online 19.20.2023 SPC lenalidomide accessed online 19.10.2023 Blueteq form accessed online 18.10.2023

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

Table 1: 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 and 2 only: 28-day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	Montelukast **Cycle 1 day 1 only**	10mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
8, 15 & 22	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections

TTO Cycle 1 and 2 only

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**40mg**	PO	OM on days **1, 8**, **15** and **22**. Taken as pre-med dose on daratumumab treatment days. Take with or after food.
	LENOLIDOMIDE	**25mg**	PO	ON on days **1** to **21.** The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
	Allopurinol	300mg	PO	OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	Omeprazole	20mg	PO	OD
	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)
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.
	Loperamide	2mg-4mg	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 then only if specified.
	Consider the use of prophylactic anti-fungals			
	Consider prophylactic anticoagulation			
	Consider levofloxacin prophylaxis for 12 weeks for all newly diagnosed myeloma patients			
	Pre med TTO packs to be dispensed			

Cycle 3 to 6 only: 28-day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
15	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections

TTO Cycle 3 to 6 only

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**40mg**	PO	OM on days **1, 8**,**15** and **22**. Taken as pre-med dose on daratumumab treatment days. Take with or after food.
	LENOLIDOMIDE	**25mg**	PO	ON on days **1** to **21.** The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
	Omeprazole	20mg	PO	OD
	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)
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.
	Loperamide	2mg-4mg	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 then only if specified.
	Consider the use of prophylactic anti-fungals			
	Consider prophylactic anticoagulation			
	Consider levofloxacin prophylaxis for 12 weeks for all newly diagnosed myeloma patients			
	Pre med TTO packs to be dispensed			

Cycles 7 onwards: 28-day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
TTO	Drug	Dose	Route	Directions	
Day 1	**DEXAMETHASONE**	**40mg**	PO	OM on days **1, 8**,**15** and **22**. Taken as pre-med dose on daratumumab treatment days. Take with or after food.	
	LENOLIDOMIDE	**25mg**	PO	ON on days **1** to **21.** The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.	
	Omeprazole	20mg	PO	OD	
	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)	
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.	
	Loperamide	2mg-4mg	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 then only if specified.	
	Consider the use of prophylactic anti-fungals				
	Consider prophylactic anticoagulation				
	Pre med TTO packs to be dispensed				