

# DARATUMUMAB WITH LENALIDOMIDE AND DEXAMETHASONE

## INDICATION

Untreated multiple myeloma when a stem cell transplant is unsuitable. Blueteq Required. (NICE TA917)

[Unfunded indication] Relapsed multiple myeloma - This combination is not funded by NHS England. Individual funding must be agreed prior to initiation.

### Key prescribing points:

- Subcutaneous route of administration of daratumumab uses fixed dosing and is the standard of care for patients.
- The intravenous route of administration uses weight-based dosing (Refer to Appendix 1) and can be used in specific clinical scenarios if required, at the clinician discretion.

## TREATMENT INTENT

Disease modification

## GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:

- FBC & film
- Clotting screen
- U&Es, LFTs, Calcium
- Albumin
- Uric acid
- ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
- Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
- Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio,
- Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
- Serum free light chain assay (Freelite)
- Transfusion assays add
- $\beta_2$  microglobulin
- 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 Genetics Laboratory (address below).
- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- Imaging as per NICE/network guidance and clinical presentation

**This is a controlled document and therefore must not be changed**

**1 of 15**

MM.38 Dara Len Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2022	V. 2.0
-----------------------	---	---------------------------	--------

Wessex Regional Genetic Laboratory  
Salisbury NHS Foundation Trust  
Salisbury District Hospital  
Salisbury  
Wiltshire  
SP2 8BJ

**Additional investigations:**

- Plasma viscosity if hyperviscosity suspected.
2. 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.
  3. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
  4. Counselling - all patients should receive verbal and written information on oral chemotherapy.
  5. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
  6. Fertility - all patients should be offered fertility advice, as appropriate.
  7. Hydration - fluid intake of at least 3 litres /day should be attempted.
  8. Document patient's height and weight, dose on actual body weight.
  9. Treatment must be agreed at the relevant MDT.

**REGIMEN SPECIFIC PRE-ASSESSMENT**

- The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.
- Clinical Assessment of thrombo-embolic risk.
- **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that patient is due to commence daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of daratumumab to red cells.**

---

**METHOD OF SUBCUTANEOUS DARATUMUMAB ADMINISTRATION:**

Inject the subcutaneous dose (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 the dose at other sites of the body as no data are available.

Injection sites should be rotated for successive injections. The subcutaneous dose should never be injected into areas where the skin is red, bruised, tender, 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.

## DRUG REGIMEN

## Cycles 1 &amp;2

Cycles 1 &2	<b>Pre-meds</b>	Montelukast 10mg PO on <b>(cycle 1 only)</b> Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg PO (with first daratumumab dose, then can be reduced to 12mg from the second dose onwards)	To be given 1 hour prior to daratumumab  Days 1, 8, 15 and 22
	<b>Daratumumab</b>	1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1, 8, 15 and 22
	<b>Post-infusion</b>	Dexamethasone 20mg mg PO	Days 2, 9,16, 23  i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
	<b>Lenalidomide</b>	The starting dose is 25 mg once daily. Dose reductions may apply see below	NOCTE, Days 1 to 21

## Cycles 3 to 6

Cycles 3 to 6	<b>Pre-meds</b>	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO/IV	To be given 1 hour prior to daratumumab  Days 1 and 15
	<b>Daratumumab</b>	1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1 and 15
	<b>Post-infusion</b>	Dexamethasone 12mg PO	Days 2 and 16  i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*  *Note: On daratumumab weeks, pre- and post-infusion dexamethasone also being used as the weekly steroid component of the triple combination regimen
	<b>Lenalidomide</b>	The starting dose is 25 mg once daily.	NOCTE, Days 1 to 21

This is a controlled document and therefore must not be changed

3 of 15

MM.38  
Dara Len Dex

Authorised by Myeloma lead Dr. Karthik Ramasamy

Review date:  
June 2022

V. 2.0

		Dose reductions may apply see below	
	<b>Dexamethasone (non-daratumumab days)</b>	40mg PO once  (The dose may be reduced in the elderly or if steroid-related side effects develop)	Days 8 and 22

**Cycle 7- Onwards**

<b>Cycles 7 onwards</b>	<b>Pre-meds</b>	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO/IV	To be given 1 hour prior to daratumumab  Day 1
	<b>Daratumumab</b>	1800mg (fixed dose) subcutaneously over 3-5 minutes	Day 1
	<b>Post-infusion</b>	Dexamethasone 8mg PO	Day 2  i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*  *Note: On daratumumab weeks, pre- and post-infusion dexamethasone also being used as the weekly steroid component of the triple combination regimen
	<b>Lenalidomide</b>	The starting dose is 25 mg once daily. Dose reductions may apply see below	NOCTE, Days 1 to 21
	<b>Dexamethasone (non-daratumumab days)</b>	40mg PO once  (The dose may be reduced in the elderly or if steroid-related side effects develop)	Days 8, 15 and 22

**CYCLE FREQUENCY**

The cycle is repeated every 28 days until disease progression.

## DOSE MODIFICATIONS

### Myelosuppression:

Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC)  $< 1.0 \times 10^9/L$ , and/or platelet count  $< 30 \times 10^9/L$ . If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

No dose adjustments are made for daratumumab.

### Recommended dose adjustments during treatment and to restart treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide alone. For other grade 3 or 4 toxicities, lenalidomide should be interrupted and restarted at the next lower dose level once toxicity has resolved to grade 2 or less.

Note: Consider re-escalating lenalidomide dose provide toxicities have completely resolved.

Starting dose = 25 mg/day.

### Thrombocytopenia:

When platelets	Recommended Course
First fall to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at 15 mg/day
For each subsequent drop below $30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

### Neutropenia:

When neutrophils	Recommended Course
First fall to $< 1.0 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to $\geq 1.0 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at 25 mg once daily
Return to $\geq 1 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at 15 mg once daily
For each subsequent drop below $< 1.0 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days.
Return to $\geq 1.0 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

**Renal/Hepatic Impairment:**

**DARATUMUMAB:**

Renal	Hepatic
No dosage adjustment is necessary for patients with pre-existing renal impairment	No formal studies of daratumumab in patients with hepatic impairment have been conducted.  Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment

**LENALIDOMIDE:**

Renal	Hepatic
CrCl 30- <50 mL/min CrCl < 30 mL/min, no dialysis CrCl < 30 mL/min, requiring dialysis	10mg once daily* 15 mg every other day** 5 mg once daily***
No formal studies. No specific dose recommendations	
*Can increase to 15mg OD if no response and patient tolerating ** Can increase to 10mg OD if no response and patient tolerating *** On dialysis day, administer dose after dialysis/	

**INVESTIGATIONS – during treatment**

- FBC, U&Es, LFTs, Ca<sup>++</sup>, glucose – every 3 - 4 weeks.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/ blood sugar

**CONCURRENT MEDICATIONS**

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Prophylactic fluconazole.
- Thromboprophylaxis/anticoagulation as above.
- Prophylactic aciclovir 200 mg bd to tds (depending on renal function).
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft. Pentamidine can be considered for patients who are intolerant or allergic to co-trimoxazole.
- Consider prophylactic laxatives to be taken if needed.
- Bone protection as per NCCN Bone Protection protocol MM.3
- Consider cholestyramine if suspicion of bile salt malabsorption

**EMETIC RISK**

Low risk.

This is a controlled document and therefore must not be changed

6 of 15

MM.38 Dara Len Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2022	V. 2.0
-----------------------	---	---------------------------	--------

## ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

The most common adverse events are neutropenia, anaemia, thrombocytopenia, upper respiratory tract infections, pneumonia, diarrhoea/constipation, fatigue and infusion reactions.

### 1- DARATUMUMAB-RELATED:

#### Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

- I. **Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.**
- II. **Patients must be screened prior to starting daratumumab.**
- III. **Transfusion alert card**

#### Interference with Determination of Complete Response

Daratumumab 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.

#### Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.

#### Infusion reactions with subcutaneous daratumumab

Daratumumab solution for subcutaneous injection can cause severe and/or serious infusion-related reactions (IRRs), including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients.

The median time to onset of IRRs following injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia.

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored 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.

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following daratumumab injection. Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

### **Other common adverse effects:**

Fatigue, allergic rhinitis, pyrexia, nasopharyngitis, URTI, cough, GI disorders (nausea, constipation, diarrhoea), headache, neutropenia and hypertension have also been reported. The most common serious adverse reactions were pneumonia, and pyrexia.

## **2- LENALIDOMIDE-RELATED**

- **Teratogenicity:** The risk management programme should be observed - see link to manufacturers data sheet on website. The concomitant use of an effective method of contraception is mandatory in all female patients of childbearing potential. Male patients should also use a condom when having sexual intercourse with women of childbearing potential. **Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.**
- **Diarrhoea:** Diarrhea was reported in 42% of patients requiring use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small % of patients of lenalidomide, and consider addition of cholestyramine
- **Venous thromboembolism (VTE):**  
 There is an increased risk of thrombosis, and some form of prophylaxis is recommended as follows:
  1. Aspirin can be appropriate for patients with no additional risk factors for thrombosis
  2. If additional risk factors consider:
    - Prophylactic low-molecular weight heparin, OR
    - Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3, OR
    - Direct oral anticoagulant e.g. apixaban for thromboprophylaxis or treatment dose as indicated.

**Aspirin is generally not preferred for higher risk patients with additional risk factors such as immobility. If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.**

- **Drowsiness, somnolence and sedation:** Take the dose at night time. Lenalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking lenalidomide.
- **Peripheral neuropathy:** Patients should be advised to report prickling, numbness and paraesthesia. Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.
- **Dizziness and orthostatic hypotension:** Patients should be advised that lenalidomide may cause orthostatic hypotension and that, if affected, they should sit upright for a few minutes prior to standing up from a recumbent position.
- **Other warnings:** Patients should be informed not to donate blood or semen during or within 8 weeks of stopping lenalidomide treatment.
- **There is an MHRA alert on an increased risk of secondary malignancies in three large trials of lenalidomide treatment.** The MHRA recommend vigilance in reporting such events promptly.

**This is a controlled document and therefore must not be changed**

**8 of 15**

MM.38 Dara Len Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2022	V. 2.0
-----------------------	---	---------------------------	--------



Quoted incidence is 3 to 4% per annum.

**TREATMENT RELATED MORTALITY**

<5%

**REFERENCES**

1. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, October 2016
2. eMC UK Summary of Product Characteristics for DARZALEX 1,800 mg solution for injection, Janssen-Cilag Ltd, Aug 2021
3. JanssenMD . 2016. DARZALEX (daratumumab) Full Prescribing Information. Online. Available at: [https://www.janssenmd.com/pdf/darzalex/DARZALEX\\_PI.pdf](https://www.janssenmd.com/pdf/darzalex/DARZALEX_PI.pdf) (last accessed: 01.02.2017)
4. Meletios A. Dimopoulos, M.D., Albert Oriol, M.D., Hareth Nahi, M.D., Jesus San-Miguel, M.D., Nizar J. Bahlis, M.D., Saad Z. Usmani, M.D., Neil Rabin, M.B., B.S., Ph.D., Robert Z. Orlowski, M.D., Mieczyslaw Komarnicki, M.D., Kenshi Suzuki, M.D., Torben Plesner, M.D., Sung-Soo Yoon, M.D., Dina Ben Yehuda, M.D., Paul G. Richardson, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Steen Lisby, M.D., Nushmia Z. Khokhar, M.D., Lisa O'Rourke, M.S.N., Christopher Chiu, Ph.D., Xiang Qin, M.S., Mary Guckert, M.S.N., Tahamtan Ahmadi, M.D., and Philippe Moreau, M.D. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. The New England Journal of Medicine. 2016. October 375 (14): 1319-1331

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung ( Specialist Cancer Pharmacist)	New document	Feb 2017	1.0	Feb 2019
Faouzi Djebbari (Haematology Pharmacist)	Updated renal and hepatic impairment, concurrent medication and references	July 2017	1.1	June 2018
Quality Manager	Nursing care plan added	May 2021	1.2	June 2018
NSSG Myeloma Group	Update from IV to SC daratumumab	October 2021	2.0	June 2022

**REVIEW**

MM.38 Dara Len Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2022	V. 2.0
-----------------------	---	---------------------------	--------

**Appendix 1: intravenous daratumumab:**

There may be a need to arrange for patient admission with the first infusion of intravenous daratumumab, where an extended duration of infusion is anticipated due to potential infusion-related reactions. Some day units are able to accommodate Cycle 1 Day 1, thus avoiding admission. Alternatively, to facilitate administration in the outpatient setting, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively

From cycle 2 onwards, patients may qualify for rapid rate intravenous infusion. See MM.48 (Daratumumab Rapid Rate Infusion) for further information.

**Cycles 1 &2**

<b>Daratumumab</b>	<p><u>Pre-meds:</u> 1 hour prior to infusion Montelukast 10mg PO on <b>(cycle 1 only)</b>, Paracetamol 1g PO, Chlorphenamine 10 mg IV, <b>Dexamethasone</b> 20mg* IV bolus or PO (can be reduced to 12mg following the second infusion)</p> <p><b>Daratumumab</b> 16mg/kg Intravenous infusion.</p> <p><u>Post-infusion:</u> <b>Dexamethasone</b> 20mg PO*</p>	<p>Days 1, 8, 15 and 22</p> <p>Days 1, 8, 15 and 22</p> <p>Days 2, 9, 16 and 23 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*</p>
	<p>*Note: Pre- and post- infusion dexamethasone is also being used as the weekly steroid component of the triple combination regime.</p>	
<b>Lenalidomide</b>	<p>The starting dose of lenalidomide is 25 mg orally once daily. Dose reductions may apply see below.</p>	<p>Days 1 to 21</p>

**Cycles 3 to 6**

<b>Daratumumab</b>	Pre-meds: 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV, <b>Dexamethasone</b> 12mg* IV bolus or PO	Days 1 and 15
	<b>Daratumumab</b> 16mg/kg Intravenous infusion.  <u>Post-infusion:</u> <b>Dexamethasone</b> 12mg PO*	Days 1 and 15  Days 2 and 16 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
*Note: On daratumumab weeks, pre- and post- infusion dexamethasone also being used as the weekly steroid component of the triple combination regime.		
<b>Dexamethasone</b>	40mg PO once weekly*	Days 8 and 22*
	(The dose may be reduced in the elderly or if steroid-related side effects develop)	
*Note: On days 1 and 15, the weekly dexamethasone dose as part of the triple combination is administered as the pre- and post-infusion steroids.		
<b>Lenalidomide</b>	The starting dose of lenalidomide is 25 mg PO once daily. Dose reductions may apply see below.	Days 1 to 21

**Cycle 7- Onwards**

<b>Daratumumab</b>	Pre-meds: 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV, <b>Dexamethasone</b> 12mg* IV bolus or PO	Day 1
	<b>Daratumumab</b> 16mg/kg Intravenous infusion.  <u>Post-infusion:</u> <b>Dexamethasone</b> 8mg PO*	Day 1  Day 2 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
*Note: On daratumumab weeks, dexamethasone is also being used as the weekly steroid component of the triplet combination regime.		
<b>Dexamethasone</b>	40mg PO once weekly*	Days 8, 15 and 22*
	(The dose may be reduced in the elderly or if steroid-related side effects develop)	
*Note: On day 1, the weekly dexamethasone dose as part of the triple combination is administered as per the pre- and post-infusion steroids.		
<b>Lenalidomide</b>	The starting dose of lenalidomide is 25 mg PO once daily. Dose reductions may apply see below.	Days 1 to 21

## INFUSION RATES

### The first dose of daratumumab must be given as an inpatient

Administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion.

	Dilution volume (Sodium chloride 0.9%)	Initial rate (first hour)	Rate increment	Maximum rate
<b>First infusion</b>	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Second infusion<sup>a</sup></b>	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Subsequent infusions<sup>b</sup></b>	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

<sup>a</sup> Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.

<sup>b</sup> Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100mL/hr in the first two infusions.

Note: For guidance on infusion rates **in the case of infusion related reactions**. See the managing infusion reactions section below.

### Infusion reactions

- Daratumumab can cause severe infusion reactions. Approximately half of all patients treated have experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.
- Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.
- Pre-meds must be given 1 hour before the infusion. Patients must be monitored during the entire infusion.
- To reduce the risk of delayed infusion reactions, corticosteroids are given to all patients on the first and second day after all infusions
- Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders.

**Managing Infusion related reactions**

For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation as outlined below.

IRR grade	Recommendation
Grade 1-2 (mild to moderate)	Once symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate.
Grade 3 (severe)	If the intensity of the reaction decreases to $\leq$ Grade 2, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate.  Permanently discontinue treatment upon the third occurrence of a Grade 3 or greater reaction.
Grade 4 (life threatening)	Permanently discontinue treatment.

**Nursing Care Plan: Daratumumab with Lenalidomide and Dexamethasone**

**Indication:** Relapsed Myeloma.

**Frequency:** Cycles are repeated every 28 days until disease progression.

**Alopecia:** No.

**On cycle 1 day 1 send phenotyping bloods to the Transfusion Lab prior to Daratumumab 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 Daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of Daratumumab to red cells.

**DARATUMUMAB:** Monoclonal human antibody.

**Administration:** Sub cutaneous injection in the abdomen, approximately 7.5cm either side of the naval. Daratumumab is not approved to be given in any other injection sites.

IV infusion is available in a small minority of circumstances; SC administration is the standard of care.

**Cycles 1-2** Daratumumab given on days 1, 8, 15 and 22.

**Cycles 3-6** Daratumumab given on day 1 and 15.

**Cycle 7 onwards** Daratumumab given on day 1 (28 day cycle).

**Emetic risk:** Minimal.

**Classification of extravasation:** Neutral.

**Side effects:** Fatigue, bone marrow depression, thrombocytopenia, risk of infection, diarrhoea, constipation, anaemia.

**Dosing reactions:** Cough, fever, nasal irritation, wheezing, bronchospasm, hypotension, laryngeal and facial oedema, and urticaria/itching, anaphylaxis.

Reactions rarely occur after the first dose. **Patients are required to remain on the unit for 4 hours following Daratumumab injection on C1D1.** No observation period is necessary for subsequent injections.

Premeds are given 1-3 hours prior to Daratumumab, patients usually take these in advance from their TTO's after C1D1.

**LENALIDOMIDE (REVLIMID):** Immunomodulator and angiogenesis inhibitor.

Administered orally on **days 1-21.**

**Emetic risk:** minimal.

**Side effects:** neutropenia, peripheral neuropathy, diarrhoea, constipation, flu like syndrome, infections, fatigue, muscle cramps, rash/itching, venous thromboembolism, bone marrow depression, drowsiness/sedation (recommended taking at night time).

**DEXAMETHASONE:** corticosteroid tablets

Administered orally each week and additionally the day after Daratumumab. Taken with or after food preferably at breakfast.

**This is a controlled document and therefore must not be changed**

**14 of 15**

MM.38 Dara Len Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2022	V. 2.0
-----------------------	---	---------------------------	--------

**Dexamethasone also acts as a premed and needs to be given at least 1 hour pre Daratumumab.**

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

### Regime Specific Considerations

- Bloods are required (including glucose) at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**
- Ensure patients have been given a Patient ID Card for Daratumumab and are instructed to carry this for 6 months after stopping treatment; please check with Myeloma CNS team.
- Inject the SC dose of Daratumumab (15 mL) into the abdomen approximately 7.5 cm to the right or left of the navel over 5 minutes. Rotate injection sites for each dose. If the patient experiences pain or discomfort the injection can be paused. If necessary the remainder of the injection can be given on the other side of the abdomen.
- Advise patients to maintain fluid intake of 2-3 litres a day and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- **IV Daratumumab only** - administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Rapid rate can be given from cycle 2 as long as there has been no reaction to the previous dose and this was given in 500mls rather than 1 litre of fluid. Montelukast needs to be given before the first rapid rate infusion.
- Montelukast is given as a premed pre SC/IV Daratumumab on C1 only.