Daratumumab SC, Lenalidomide and dexAMETHasone Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Daratumumab in combination with lenalidomide and dexAMETHasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.	C90	00854	Daratumumab: ODMS 01/06/2024 Lenalidomide: CDS

* This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The dosing schedule for daratumumab (which is administered as a subcutaneous [SC] injection) in combination with lenalidomide and dexAMETHasone is based on a 28 day cycle regimen as detailed in the treatment table below (Table 1).

Treatment is continued until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment table for daratumumab, lenalidomide and dexAMETHasone

Cycle 1-2 (week 1-8, total of 8 doses of daratumumab)					
Day	**Drug**	**Dose**	**Route**	**Diluent and Rate**	**Cycle frequency**
1, 8, 15, 22	Daratumumab[a]	1800mg	SC	Over 3 to 5 minutes	28 days
1-21 (no treatment days 22-28)	Lenalidomide[b]	25mg	PO	n/a	28 days
1, 8, 15, 22	dexAMETHasone[c]	40mg	PO	n/a	28 days
Cycle 3-6 (week 9-24, total of 8 doses of daratumumab)					
Day	**Drug**	**Dose**	**Route**	**Diluent and Rate**	**Cycle frequency**
1, 15	Daratumumab[a]	1800mg	SC	Over 3 to 5 minutes	28 days
1-21 (no treatment days 22-28)	Lenalidomide[b]	25mg	PO	n/a	28 days
1, 8, 15, 22	dexAMETHasone[c]	40mg	PO	N/A	28 days
Cycle 7 onwards (week 25 onwards)					
Day	**Drug**	**Dose**	**Route**	**Diluent and Rate**	**Cycle frequency**
1	Daratumumab[a]	1800mg	SC	Over 3 to 5 minutes	28 days
1-21 (no treatment days 22-28)	Lenalidomide[b]	25mg	PO	N/A	28 days
1, 8, 15, 22	dexAMETHasone[c]	40mg	PO	N/A	28 days
[a] If a planned dose of daratumumab is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.					
[b] Lenalidomide capsules should be taken at about the same time each day, in the evening may be preferred due to risk of drowsiness. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose of lenalidomide, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.					
[c] A reduced dose of 20 mg/week may be considered for patients >75 years.					

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Adequate haematological, renal and liver function

EXCLUSIONS:

- Hypersensitivity to daratumumab, lenalidomide, dexAMETHasone or to any of the excipients
- Pregnancy
- Breast Feeding
- Severe uncontrolled asthma/obstructive airways disease
- Patients who are unable to comply with the Lenalidomide Pregnancy Prevention Programme

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Blood pressure, blood glucose (patients on oral hypoglycaemics)
- Assessment of peripheral neuropathy status
- VTE risk assessment
- Urine pregnancy testing or serum hCG test for women of childbearing potential as per Pregnancy Prevention Programme
- Assessment and registration as per Pregnancy Prevention Programme for both male and female patients
- Uric acid
- Inform patient and transfusion laboratory that patient is due to commence daratumumab. Send a 'Group and Save' sample to the transfusion laboratory for red cell phenotyping as all cross matching will be positive following treatment with daratumumab due to binding of daratumumab to red cells.
- Virology screen - EBV, CMV, Hepatitis B (HBsAg, HBcoreAb), Hepatitis C and HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC every week for first 8 weeks of treatment and then monthly
- Renal, liver and bone profile
- Blood pressure
- Blood glucose* if being treated with oral hypoglycaemics (* See Drug Interactions)
- Urine pregnancy testing or serum hCG test every 28 days for women of childbearing potential as per Pregnancy Prevention Programme
- Consider monitoring thyroid function tests

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Daratumumab:

- No dose reductions of daratumumab are recommended

Lenalidomide:

- Lenalidomide treatment must not be started if the ANC is < 1.0 x 10^9/L and/or platelets < 75x 10^9 /L
- Dosing is continued or modified based upon clinical and laboratory findings
- For haematological dose modifications, refer to Tables 2, 3 and 4 below
- The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10mg once daily
- For Grade 3 or 4 non-hematological and non-renal toxicities judged related to lenalidomide alone, treatment with lenalidomide should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and dexAMETHasone may continue.

Haematological:

Lenalidomide dose reduction steps

Dose adjustments, as summarised in Table 2, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Table 2: Dose reduction steps for lenalidomide

Dose level	Lenalidomide	dexAMETHasone
Starting dose	25mg	40mg
Dose level -1	20mg	20mg
Dose level -2	15mg	12mg
Dose level- 3	10mg	8mg
Dose level- 4	5mg	4mg
Dose level- 5	2.5mg	N/A

Table 3: Dose reduction based on thrombocytopenia

Platelets	Action
Fall to < 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide, follow with weekly FBC Resume lenalidomide at the next lower dose
For each subsequent drop to <30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at the next lower dose

Table 4: Dose reduction based on neutropenia

Neutrophils	Action
1st fall to < 1.0 x 10^9/L Return to ≥ 1.0 x 10^9/L (where no other haematological toxicity observed)	Interrupt lenalidomide therapy Resume lenalidomide at starting dose once daily
Return to ≥ 1.0 x 10^9/L (where other haematological toxicity observed)	Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 1.0 x 10^9/L Return to ≥ 1.0 x 10^9/L	Interrupt lenalidomide therapy Resume lenalidomide at dose level -1 once daily
In the case of neutropenia, the use of growth factors in patient management should be considered.	

Renal and Hepatic Impairment:

Table 5: Dose modification for renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Daratumumab[a]	No dose adjustment is needed. Haemodialysis: No need for dose adjustment is expected.		No dose adjustment is needed
Lenalidomide[b]	**CrCl (mL/min)**	**Dose modification**	No need for dose adjustment is expected
	30 to <50	Reduce dose to 10mg once daily*	
	<30 not requiring dialysis	15mg every other day	
	<30 requiring dialysis	Reduce dose to 5mg once daily. On dialysis days, dose should be administered after dialysis.	
	*The dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment		

[a] Daratumumab: Renal and hepatic from Giraud et al
[b] Lenalidomide: Renal from SPC, hepatic from Giraud et al

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

Daratumumab: Minimal **(Refer to local policy)**
Lenalidomide: Minimal to low **(Refer to local policy)**

PRE AND POST INJECTION MEDICATIONS:

- Pre-dose medications consisting of corticosteroid, anti-pyretic and anti-histamines should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every dose of daratumumab as suggested in Table 6
- When dexAMETHasone is the background-regimen specific corticosteroid, the dexAMETHasone treatment dose will instead serve as pre-medication on daratumumab dosing days. Additional background regimen specific corticosteroids (e.g. predniSONE) should not be taken on daratumumab dosing days when patients have received dexAMETHasone as a pre-medication
- If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued
- See other supportive care for recommended post-injection medications

Table 6: Suggested medications for pre and post daratumumab administration

Day	Drugs	Dose	Route	Timing	Cycle
1, 8, 15,22	dexAMETHasone	**Refer to Table 1: Treatment table for daratumumab, lenalidomide and dexAMETHasone[a]**			1-2
2, 9, 16, 23	dexAMETHasone	4mg	PO	Once daily	1[b]
2, 9, 16, 23	dexAMETHasone	4mg	PO	Once daily	2 **(only if required[b])**
1, 15	dexAMETHasone	**Refer to Table 1: Treatment table for daratumumab, lenalidomide and dexAMETHasone[a]**			3-6
2, 16	dexAMETHasone	4mg	PO	Once daily	3-6 **(only if required[b])**
1	dexAMETHasone	**Refer to Table 1: Treatment table for daratumumab, lenalidomide and dexAMETHasone[a]**			From cycle 7 onwards
2	dexAMETHasone	4mg	PO	Once daily	From cycle 7 onwards **(only if required[b])**
1, 8, 15, 22	Paracetamol	1g	PO	1-3 hours prior to daratumumab injection	1-2
1, 15	Paracetamol	1g	PO	1-3 hours prior to daratumumab injection	3 -6
1	Paracetamol	1g	PO	1-3 hours prior to daratumumab injection	From cycle 7 onwards
1, 8, 15, 22	Chlorphenamine[c]	4mg	PO	1-3 hours prior to daratumumab injection	1-2
1, 15	Chlorphenamine[c]	4mg	PO	1-3 hours prior to daratumumab injection	3 -6
1	Chlorphenamine[c]	4mg	PO	1-3 hours prior to daratumumab injection	From cycle 7 onwards
[a] **Note. On the days of daratumumab administration, the scheduled treatment dose of dexAMETHasone will be administered as a premedication prior to infusion.**					
[b] The dose of oral dexAMETHasone given on the day following the daratumumab injection (i.e. days 2,9,16 and 23) can be stopped from cycle 2 onwards if no infusion reactions occur at the discretion of the prescribing Consultant.					
[c] Or equivalent oral or intravenous antihistamine.					

OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation **(Refer to local policy)**
- Bisphosphonates should be considered in all patients with myeloma related bone disease
- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- H2 antagonist or proton pump inhibitor **(Refer to local policy)**
- Consider PJP prophylaxis **(Refer to local policy)**
- Influenza vaccination in appropriate patients
- Recommended post-injection medications for patients with a history of obstructive pulmonary disorder:
  - The use of post-injection medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered
  - Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician
- Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment

- In case of neutropenia, the consultant may consider the use of growth factors in patient management
- Thromboprophylaxis: Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicine options include single agent aspirin, or prophylactic doses of low molecular weight heparin (LMWH) or direct oral anti-coagulant (DOAC) **(Refer to local policy)**
- Prophylactic laxatives to prevent lenalidomide induced constipation **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatitis B Reactivation:** HBV screening should be performed in all patients before initiation of treatment. Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, liaise with local hepatology/infectious diseases services regarding PCR testing and appropriate anti-viral prophylaxis. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of treatment. Manage patients according to current clinical guidelines.

Daratumumab:

- **Interference with Indirect Antiglobulin Test (Indirect Coombs Test):** Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask 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. Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time. In the event of a planned transfusion, blood transfusion centres should be notified of this interference with indirect antiglobulin tests. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.
- **Interference with determination of Complete Response:** Daratumumab is a human IgG kappa monoclonal antibody that can be detected 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 some patients with IgG kappa myeloma protein.
    - Consider use of daratumumab-specific IFE reflex assay (DIRA) to distinguish the therapeutic from the patient's M protein. The DIRA assay can be used to determine whether additional testing, including determination of the sFLC ratio and BM evaluation, is warranted in patients with IgG-κ band and low measurable M protein (≤2 g/L) to assess the presence of (stringent) CR.

Lenalidomide:

- **Lenalidomide is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**
- **Teratogenetic effects:** Lenalidomide is structurally related to thalidomide, a powerful human teratogen. Lenalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Lenalidomide Pregnancy Prevention Programme are met. These conditions must be fulfilled for all male and female patients.
- **Skin reactions:** Lenalidomide must be discontinued permanently for angioedema, anaphylactic reaction, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or toxic epidermal necrolysis (TEN) is suspected. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity.
- **Cardiovascular:** Patients with known risk factors for MI, including prior thrombosis, should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia). There is an increased risk of venous and arterial thromboembolism in patients treated with lenalidomide and dexAMETHasone. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thromboembolic risk in these patients. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.
- **Peripheral neuropathy:** Lenalidomide is structurally related to thalidomide which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with lenalidomide in combination with dexamethasone OR melphalan and prednisone OR lenalidomide monotherapy OR with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.
- **Thyroid function:** Cases of hypothyroidism have been reported and baseline and ongoing monitoring of thyroid function is recommended.
- **Tumour lysis syndrome:** Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

DexAMETHasone

- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:

- No interaction studies have been performed with daratumumab.
- Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexAMETHasone
- There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

- Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources.
- Prescribers are required to read and understand the relevant HCP Information Guide and to adhere to the PPP.

REFERENCES:

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2. Facon T et al; MAIA Trial Investigators. Daratumumab plus Lenalidomide and DexAMETHasone for Untreated Myeloma. N Engl J Med. 2019 May 30; 380 (22):2104-2115. doi: 10.1056/NEJMoa1817249. PMID: 31141632; PMCID: PMC10045721.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Daratumumab (Darzalex®) SmPC. Last updated 22/03/2023. Accessed Nov 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf
6. Lenalidomide (Revlimid®) SmPC. Last updated 20/10/2023. Accessed Nov 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/06/2024		Dr Patrick Hayden
2	17/06/2024	Corrected typo in treatment table re dexamethasone route of administration. Updated lenalidomide emetogenic potential.	Dr Patrick Hayden

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.