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

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, c]	25mg	PO	N/A	28 days
1, 8, 15, 22	dexAMETHasone[d]	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, c]	25mg	PO	N/A	28 days
1, 8, 15, 22	dexAMETHasone[d]	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, c]	25mg	PO	N/A	28 days
1, 8, 15, 22	dexAMETHasone[d]	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 lenalidomide dose of 15mg, 10mg or 5mg once daily should be considered in patients >75 years especially in the context of renal impairment

[d] A reduced dose of 10-20 mg/week is advised for patients >75 years.

ELIGIBILITY:

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

CAUTIONS:

- Severe uncontrolled asthma/obstructive airways disease

EXCLUSIONS:

- Hypersensitivity to daratumumab, lenalidomide, dexAMETHasone or to any of the excipients
- Pregnancy
- Breastfeeding
- 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
- Thyroid function test
- 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 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
- 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-haematological 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 Available on the NCCP website

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

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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
- Male patients must use condoms during treatment, during dose interruption and for at least 7 days following discontinuation of lenalidomide if their partner is pregnant or is of childbearing potential not using effective contraception. Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of lenalidomide.
- 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).**
- Both diarrhoea and constipation are common side effects associated with lenalidomide treatment. Patients may require either laxatives or anti-diarrhoeals. **(Refer to local policy).**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.
- **Teratogenicity:** 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.
- **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.**
- **Venous and arterial thromboembolic events**: Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

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

Lenalidomide:

- 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. V6 2025. 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 10/04/2025. Accessed May 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf
6. Lenalidomide (Revlimid®) SmPC. Last updated 08/01/2024. Accessed May 2025. 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
3	25/09/2024	Steroid footnote amended in treatment table	Dr Patrick Hayden
4	24/09/2025	Reviewed. Steroid footnote in treatment table amended, reduced lenalidomide dosing footnote added. Severe uncontrolled asthma/obstructive airways disease moved from Exclusions to Cautions. Thyroid function test added to baseline tests. Other supportive care section updated. Regimen updated throughout in line with NCCP standardisation.	Dr Patrick Hayden

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.