

Lenalidomide 25mg and Dexamethasone Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant	C90	00218a	
Treatment of multiple myeloma in adult patients who have received at least one prior therapy	C90	00218b	CDS

**If the reimbursement status is not defined¹, the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

Lenalidomide is taken orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is taken orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Treatment is continued until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Cycle
1-21 (no treatment days 22-28)	Lenalidomide	25mg/day	PO*	All cycles
1,8, 15 and 22**	Dexamethasone	40mg	PO	All cycles
<p>*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.</p>				
<p>**Dexamethasone dosing may alternately be given D1-4, 9-12, 17-20 on cycles 1-4 in patients who have received prior therapy. This is to be determined by the treating consultant.</p>				

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to lenalidomide or any of the excipients.
- Pregnancy.
- Women of childbearing potential unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met.

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.

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- Blood pressure, blood glucose (patients on oral hypoglycaemics).
- Assessment of peripheral neuropathy status.
- VTE risk assessment.
- Pregnancy test in women of child bearing age or evidence of a hysterectomy. Assessment and registration as per Pregnancy Prevention Program for both male and female patients.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV
Hepatitis B Reactivation: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy, for the entire duration of chemotherapy and for six months afterwards (Refer to local policy). Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

Regular tests:

- FBC every week for first 8 weeks of treatment and then monthly,
- Renal, liver and bone.
- Blood pressure
- Blood glucose* if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Pregnancy test every 28 days if female of childbearing potential.
- 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.
- Lenalidomide treatment must not be started if the ANC is < 1.0 x 10⁹/L and/or platelets < 75 x 10⁹/L
- Dosing is continued or modified based upon clinical and laboratory findings.
- The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10mg once daily.

Haematological:

Dose reduction Steps

Dose adjustments, as summarized in Table 1, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia , or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Table 1: Dose reduction steps for lenalidomide and dexamethasone

	Lenalidomide	Dexamethasone
Starting dose	25mg	40mg
Dose level -1	20mg	20mg

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Dose level -2	15mg	12mg
Dose level- 3	10mg	8mg
Dose level- 4	5mg	4mg
Dose level- 5	2.5mg	NA

Table 2: Dose reduction based on thrombocytopenia

Platelets	Action
Fall to $< 25 \times 10^9/L$	Stop lenalidomide dosing for remainder of cycle ^a
Return to $\geq 50 \times 10^9/L$	Decrease by one dose level when dosing resumed at next cycle

^aIf Dose Limiting Toxicity (DLT) occurs on > Day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

Table 2: Dose reduction based on neutropenia

Neutrophils	Action
1 st fall to $< 0.5 \times 10^9/L$	Interrupt lenalidomide therapy
Return to $\geq 1.0 \times 10^9/L$ (where no other haematological toxicity observed)	Resume lenalidomide at starting dose once daily
Return to $\geq 0.5 \times 10^9/L$ (where other haematological toxicity is observed)	Resume lenalidomide at dose level -1 once daily
For each subsequent drop $< 0.5 \times 10^9/L$	Interrupt lenalidomide therapy
Return to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at next lower dose level (dose level 2 or 3). Minimum dose level ≥ 5 mg daily

In the case of neutropenia, the use of growth factors in patient management should be considered

If the dose of lenalidomide was reduced for a haematologic dose limiting toxicity (DLT), the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) at the discretion of the treating consultant if continued lenalidomide/dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC $> 1.5 \times 10^9/L$ with a platelet count $> 100 \times 10^9/L$ at the beginning of a new cycle at the current dose level).

Renal and hepatic impairment:

Table 3: Dose modification of lenalidomide for hepatic and renal impairment

Renal Impairment		Hepatic Impairment
Creatinine Clearance ml/min	Dose modification	Dose Modification
30 to 50	Reduce dose to 10mg once daily*	No specific dose recommendations as lenalidomide has not formally been studied in patients with impaired hepatic function
<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		

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS: Not usually required.

OTHER SUPPORTIVE CARE:

- In case of neutropenia, the consultant may consider the use of growth factors in patient management.
- Thromboprophylaxis (Refer to local policy)
- Prophylactic laxatives to prevent lenalidomide induced constipation (Refer to local policy).
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H₂ antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy (Refer to local policy).
- Tumour Lysis Syndrome prophylaxis (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.

- **Teratogenic effects:** Lenalidomide is structurally related to thalidomide a powerful human teratogen. It must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met.
- **Skin reactions:** Lenalidomide must be discontinued permanently for exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected.
- **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. The neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.
- **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.

DRUG INTERACTIONS:

- 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,

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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.

ATC CODE:

Lenalidomide - L04AX04

COMPANY SUPPORT RESOURCES/Useful Links:

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

http://celgene.co.uk/content/uploads/sites/3/Revlimid_Prescription_Authorisation_Form.pdf

REFERENCES:

1. Palumbo A, Hajek R et al. Continuous Lenalidomide treatment for Newly Diagnosed Multiple Myeloma. *New Eng J Med* 2012;366:1759-1769.
2. Palumbo A, Rajkumar SV, Dimopoulos MA et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008;22:414-23.
3. Rajkumar SV, Jacobus S et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 2010;11(1):29-37.
4. Revlimid® (Lenalidomide) EMA SmPC Last updated: 22/01/2019 Accessed Apr 2019. Available at https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	02/05/2017		Dr Patrick Hayden, Dr John Quinn
2	19/06/2019	Updated recommendation on Hep B reactivation	Dr Patrick Hayden, Dr John Quinn

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;

<http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

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