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

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 once daily	PO[1]	Continuous
1,8, 15 and 22[2]	dexAMETHasone	40mg once daily	PO	Continuous

[1]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.

[2]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.

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to lenalidomide or any of the excipients
- Pregnancy
- 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
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), 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
- Lenalidomide treatment must not be started if the ANC is < 1.0 x 10^9/L and/or platelets < 75 x 10^9/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 summarised 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
Dose level -2	15mg	12mg
Dose level- 3	10mg	8mg
Dose level- 4	5mg	4mg
Dose level- 5	2.5mg	N/A

Table 2: Dose reduction based on thrombocytopenia

Platelets	Action
Fall to <25 x 10^9/L Return to ≥ 50 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a] Decrease by one dose level when dosing resumed at next cycle
[a]If 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 3: Dose reduction based on neutropenia

Neutrophils	Action
1st fall to < 0.5 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 ≥ 0.5 x 10^9/L (where other haematological toxicity is observed)	Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 0.5 x 10^9/L Return to ≥ 0.5 x 10^9/L	Interrupt lenalidomide therapy Resume lenalidomide at next lower dose level (dose level -2 or -3). Minimum dose level ≥ 5mg 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 x 10^9/L with a platelet count > 100 x 10^9/L at the beginning of a new cycle at the current dose level).	

Renal and hepatic impairment:

Table 4: 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*	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations
<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		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to 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: 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).**
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H_2 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.

This medicinal product 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 interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued permanently for angioedema, anaphylactic reaction, Grade 4 rash, 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.
- **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. (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.

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, 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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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. 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. Lenalidomide (Revlimid®) EMA SmPC. Last updated 02/03/2023. Accessed June 2023. 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
3	20/11/2023	Reviewed. Amended treatment table and emetogenic potential. Added standardised wording for lenalidomide PPP. Added to adverse effects (Skin reactions, peripheral neuropathy and Hepatitis B reactivation). Updated supportive care section company resources	Dr Patrick Hayden, Prof John Quinn

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.