Lenalidomide Maintenance Therapy (RVD-Lite)[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Indicated as single agent maintenance therapy in patients with newly diagnosed multiple myeloma patients who are transplant ineligible after completion of RVD-lite induction and consolidation therapy.	C90	00782a	

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 administered as maintenance treatment, at the discretion of the prescribing consultant, after completion of RVD-Lite induction treatment **(Please refer to NCCP Regimen 00780 Bortezomib, Lenalidomide and Dexamethasone (RVD-lite) Induction Therapy)** and RVD-Lite consolidation treatment **(Please refer to NCCP Regimen 00781 Bortezomib and Lenalidomide RVD-Lite Consolidation Therapy)**.
Treatment is continued until disease progression or unacceptable toxicity.

Day	Drug	Dose	Route	Cycle
1-21 inclusive	Lenalidomide	15mg	PO[a]	Every 28 days

[a] 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.

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to lenalidomide or to any of the excipients
- Pregnancy
- Patients who are unable to comply with the Lenalidomide Pregnancy Prevention Programme
- Grade ≥2 peripheral neuropathy
- ANC < 1 x 10^9 cells/L

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 Program for both male and female patients
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C and HIV ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

Regular tests:

- FBC; monitor platelet count at a minimum of day 1
- Liver, renal, bone profile
- Blood pressure
- 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
- Blood glucose* if being treated with oral hypoglycaemics **(*See Drug Interactions)**

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 or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9 /L**.**
- Dose level reductions for lenalidomide are described in Table 1 below.

Table 1: Dose reduction steps for lenalidomide

Dose level	**Lenalidomide**
Starting dose	15mg
Dose level -1	10mg
Dose level -2	5mg
Dose level -3	Discontinue

Haematological:

Table 2: Dose Modifications for Thrombocytopenia

Platelets	Lenalidomide
First Fall to < 30 x 10^9/L	Interrupt lenalidomide therapy
Return to ≥30x10^9/L	Resume lenalidomide at dose level -1
For each subsequent drop to < 30 x 10^9/L	Interrupt lenalidomide therapy
Return to ≥30x10^9/L	Resume lenalidomide at next lower dose level once daily. Do not dose below 5mg once daily

Table 3: Dose Modifications for neutropenia

ANC	Lenalidomide
First fall to < 0.5 x 10^9/L Return to ≥ 0.5x10^9/L (where no other haematological toxicity is observed)	Interrupt lenalidomide therapy Resume lenalidomide at starting dose once daily
Return to ≥ 0.5x10^9/L (where other haematological toxicity is observed)	Resume lenalidomide at dose level -1
For each subsequent drop to <0.5 x 10^9/L	Interrupt lenalidomide therapy
Return to ≥ 0.5x10^9/L	Resume lenalidomide at next lower dose level once daily. Do not dose below 5mg once 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 haematological 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 in Renal or Hepatic Impairment

Drug	Renal impairment		Hepatic impairment
Lenalidomide	**Creatinine Clearance ml/min**	**Dose modification**	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.
	30 to 50	Reduce dose to 10mg once daily[a]	
	<30 not requiring dialysis	15mg every other day	
	< 30 requiring dialysis	5mg once daily. On dialysis days the dose should be administered following dialysis.	
	[a]The dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment		

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

**ULN = Upper Limit Normal

Dose reductions for other toxicities:

Table 5: Dose Modification of Lenalidomide for Adverse Events

Drug	Adverse reactions*	Recommended dose modification
Lenalidomide	Thromboembolic event	Withhold treatment and start standard anticoagulant therapy. Once stabilised on the anticoagulant therapy and complications of thromboembolic event have been managed, lenalidomide treatment may be restarted at the original dose dependant on a benefit/risk assessment. Anticoagulant therapy should be continued during the course of lenalidomide treatment.
	Skin rash	Withhold treatment and evaluate clinically. If allergic reaction do not resume treatment.
	Angioedema	Discontinue treatment.

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Lenalidomide: Minimal to Low (**Refer to local policy**).

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment.

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
- 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.

- **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 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.
- **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:

- 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

Educational materials – HCP and Patient
https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results/item?pano=EU/1/07/391/002&t=Revlimid

REFERENCES:

1. O'Donnell, K et al. A Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Ineligible Multiple Myeloma – Phase 2 study Br J Haematol. 2018 July
2. Cook et al. Outcomes with different administration schedules of bortezomib in bortezomib, lenalidomide and dexamethasone (VRd) as first-line therapy in multiple myeloma. American Journal of hematology 2020: 26074
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
4. Lenalidomide (Revlimid®) Summary of Product Characteristics EMA. Last updated 07/01/2022. Accessed Sept 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	02/11/2022		NCCP Plasma Cell Disorder Clinical Advisory Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.