Bortezomib, Lenalidomide and dexAMETHasone (RVD-Lite) Induction Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of newly diagnosed multiple myeloma patients who are transplant ineligible.	C90	00780a	N/A

* 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.

Bortezomib is administered once weekly on days 1, 8, 15 and 22; dexAMETHasone on days 1, 2, 8, 9, 15, 16 and 22 and 23; and lenalidomide on days 1-21 of a 35 day treatment cycle for up to nine cycles or until disease progression or unacceptable toxicity occurs. This is the induction phase.

The induction phase is followed by six cycles of consolidation therapy **(Please refer to NCCP Regimen 00781 Bortezomib and Lenalidomide RVD-Lite Consolidation Therapy)**.

Lenalidomide only may be continued as maintenance therapy, at the discretion of the prescribing consultant **(Please refer to NCCP Regimen 00782 Lenalidomide RVD-Lite Maintenance Therapy).**

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

Day	Drug	Dose	Route	Cycle
1, 8, 15 and 22	Bortezomib[a]	1.3mg/m^2	SC[b, c] (abdomen or thigh)	Every 35 days for up to 9 cycles
1-21 inclusive	Lenalidomide	15mg	PO[d]	Every 35 days for up to 9 cycles
1, 2, 8, 9, 15, 16, 22 and 23	dexAMETHasone[e]	20mg	PO[f]	Every 35 days for up to 9 cycles
[a] Bortezomib is a proteasome inhibitor and is neurotoxic. Refer **to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer** Here.				
[b] In individual cases where approved by Consultant bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/mL when administered via the IV route.				
[c] The solution should be injected subcutaneously, at a 45-90^0 angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered SC or a switch to IV injection is recommended. At least 72 hours should elapse between consecutive doses of bortezomib.				

[d] 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.
[e] Patients >75 years to take dexAMETHasone on days 1, 8, 15 and 22 only.
[f] dexAMETHasone to be taken once daily in the morning with food.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- ECOG 0-2; ECOG>2, at consultant discretion
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy.

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, lenalidomide, dexAMETHasone or any of the excipients
- Grade ≥ 2 peripheral neuropathy
- ANC < 1 x 10^9 cells/L; for ANC < 1 x 10^9 cells/L, therapy at consultant discretion, if neutropenia deemed to be related to bone marrow infiltrate by disease
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
- Patients who are unable to comply with the Lenalidomide Pregnancy Prevention Programme
- Breastfeeding

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
- Uric acid
- Clotting screen
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. **(* See Drug Interactions)**

- 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 Regimen Specific Complications re Hepatitis B Reactivation**

Regular tests:

- FBC; monitor platelet count at a minimum of day 1 and day 15 each cycle
- 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 pressure, *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
- Bortezomib therapy should be withheld when the platelet count is < 25 x 10^9/L
- Dose level reductions for bortezomib and lenalidomide are described in Table 1 below

Table 1: Dose reduction steps for lenalidomide and bortezomib

Dose Level	Lenalidomide	Bortezomib
Starting dose	15mg	1.3mg/m^2
Dose level -1	10mg	1.0mg/m^2
Dose level -2	5mg	0.7mg/m^2
Dose level -3	Discontinue	Discontinue

Haematological:

Table 2: Dose Modifications for Thrombocytopenia

Platelets (x 10^9/L)	Lenalidomide	Platelets (x 10^9/L)	Bortezomib
First Fall to < 30	Interrupt lenalidomide therapy	≥25	Maintain full dose
Return to ≥ 30	Resume lenalidomide at dose level -1 once daily		
For each subsequent drop to < 30	Interrupt lenalidomide therapy	<25	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at the next lower dose level. If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
Return to ≥ 30	Resume lenalidomide at next lower dose level once daily. Do not dose below 5mg once daily		

Table 3: Dose Modifications for neutropenia

ANC (x 10^9/L)	Lenalidomide	ANC (x 10^9/L)	Bortezomib
First fall to < 0.5 Return to ≥ 1 (where no other haematological toxicity is observed)	Interrupt lenalidomide therapy; Resume lenalidomide at starting dose once daily	≥ 0.5	Maintain full dose
Return to ≥ 0.5 (where other haematological toxicity is observed)	Resume lenalidomide at dose level -1		
For each subsequent drop to < 0.5	Interrupt lenalidomide therapy	< 0.5	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at the next lower dose level. If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
Return to ≥ 0.5 x 10^9/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 Bortezomib and Lenalidomide in renal and hepatic Impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="6">Bortezomib</td><td colspan="2" rowspan="6">Renal impairment: No dose adjustment is needed.

Haemodialysis: No dose adjustment is needed, administer after haemodialysis.</td><td>Grade of Hepatic Impairment</td><td>Bilirubin Level</td><td>(AST) Levels</td><td>Modification of starting dose</td></tr>
<tr><td rowspan="2">Mild</td><td>≤ 1 x ULN</td><td>> ULN</td><td>None</td></tr>
<tr><td>> 1 - 1.5 x ULN</td><td>Any</td><td>None</td></tr>
<tr><td>Moderate</td><td>> 1.5 – 3 x ULN</td><td>Any</td><td rowspan="3">Reduce dose to 0.7mg/m^2 in the first treatment cycle.
Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.</td></tr>
<tr><td>Severe</td><td>> 3 x ULN</td><td>Any</td></tr>
<tr><td></td></tr>
<tr><td rowspan="5">Lenalidomide</td><td>CrCl mL/minute</td><td>Dose modification</td><td colspan="4" rowspan="5">No need for dose adjustment is expected.</td></tr>
<tr><td>30 to 50</td><td>Reduce dose to 10mg once daily[a]</td></tr>
<tr><td>< 30 not requiring dialysis</td><td>15mg every other day</td></tr>
<tr><td>< 30 requiring dialysis</td><td>5mg once daily. On dialysis days the dose should be administered following dialysis.</td></tr>
<tr><td colspan="2">[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</td></tr>
<tr><td colspan="6">[a] Bortezomib (renal - Giraud et al 2023; hepatic - SPC)
[b] Lenalidomide (renal – SPC; hepatic – Giraud et al 2023)</td></tr>
</table>

Neuropathic pain and/or peripheral neuropathy:

Table 5: Dose modifications for Bortezomib Related Neuropathy

Severity of neuropathy	Dose Modification
Grade 1 with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
Grade 4 and/or severe autonomic neuropathy	Discontinue treatment
Grade 1: Asymptomatic; loss of deep tendon reflexes or paresthesia Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living (ADL) Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated *Grading based on NCI Common Toxicity Criteria CTCAE v 4*	

Dose reductions for other toxicities:

Table 6: Dose Modification of Bortezomib and Lenalidomide for Adverse Events

Drug	Adverse reactions*	Recommended dose modification
Bortezomib	Grade 3 Non-haematological toxicity	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at the next lower dose level. If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
	New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
	Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue treatment.
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:

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

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

For information:

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

- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Haemato-oncology) - link here

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: 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 treatment. Patients may require either laxatives or anti-diarrhoeals. **(Refer to local policies)**
- Bisphosphonates should be considered in all patients with myeloma related bone disease
- H_2-antagonist or PPI in patients receiving dexAMETHasone therapy (**Refer to local policy**)
- Consider PJP prophylaxis (**Refer to local policy**)
- Tumour Lysis Syndrome prophylaxis (**Refer to local policy**)
- Low dose antiviral prophylaxis (**Refer to local policy**)

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

- **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:

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

COMPANY SUPPORT RESOURCES/Useful Links:

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:

1. O'Donnell EK et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. Br J Haematol. 2018 Jul;182(2):222-230. doi: 10.1111/bjh.15261. Epub 2018 May 8. PMID: 29740809; PMCID: PMC6074026.
2. Rajkumar S, et al. Optimising bortezomib in newly diagnosed multiple myeloma. Lancet Oncol 2010; 11:909-10.
3. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. Lancet Oncol. 2011;12(5):431- 40.
4. Moreau P, Coiteux V, Hulin C, et al. Prospective Comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. Haematologica 2008;93:1908-11.
5. Cook J et al. Outcomes with different administration schedules of bortezomib in bortezomib, lenalidomide and dexamethasone (VRd) as first-line therapy in multiple myeloma. Am J Hematol. 2021 Mar 1; 96(3):330-337. doi: 10.1002/ajh.26074. Epub 2021 Jan 13. PMID: 33326116.
6. 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/
7. 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
8. Lenalidomide Summary of Product Characteristics EMA. Last updated 08/01/2024. Accessed 16/02/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf
   Bortezomib Summary of Product Characteristics EMA. Last updated 04/06/2021. Accessed 16/02/2024. Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	02/11/2022		NCCP Plasma Cell Disorder Clinical Advisory Group
1a	13/02/2024	Updated company support resources/ useful links section in line with NCCP standardisation.	NCCP
2	18/07/2024	Regimen reviewed. Updated Eligibility, Exclusions, Baseline and Regular Tests. Updated Tables 3, 4 and 5. Added to Other Supportive Care. Updated Adverse events/regimen specific complications and drug interactions section in line with NCCP standardisation.	Dr Janusz Krawczyk

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is an unlicensed posology for the use of bortezomib and lenalidomide in Ireland. Patient's should be informed of this 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 fully aware of their responsibility in communicating any relevant information to the patient and also 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