Bortezomib, Lenalidomide and dexAMETHasone (RVD) Therapy- 21 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of newly diagnosed myeloma in adult patients	C90	00416a	Bortezomib:N/A Lenalidomide:CDS
Treatment of relapsed or refractory myeloma that has received prior therapy in adult patients	C90	00416b	Bortezomib:N/A Lenalidomide:CDS

*This applies to 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 and 15, dexAMETHasone on days 1, 8 and 15 and lenalidomide on days 1-14 in a 21 day treatment cycle for up to eight treatment cycles or until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route	Cycle
1, 8 and 15	[a,]Bortezomib	1.3mg/m^2	[b,c]SC (abdomen or thigh)	Every 21 days for up to 8 cycles
1-14 inclusive	Lenalidomide	25mg once daily	[d]PO	Every 21 days for up to 8 cycles
1,8 and 15	dexAMETHasone	40mg once daily	[e]PO	Every 21 days for up to 8 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 Available on the NCCP website .

[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.

[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] dexAMETHasone to be taken 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
- 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
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
- Patients who are unable to comply with the conditions of 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 if being treated with 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 Regimen Specific Complications re Hepatitis B Reactivation**

Regular tests:

- FBC; monitor platelet count at a minimum of day 1 and day 11 each cycle
- Renal, liver and bone profile
- Blood pressure
- Urine pregnancy testing or serum hCG test every 28 days for women of childbearing potential as per Lenalidomide Pregnancy Prevention Programme
- Consider monitoring thyroid function tests
- Blood glucose if being treated with oral hypoglycaemics

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.
- Bortezomib therapy should be withheld when the platelet count is < 25 x 10^9/L.

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

	Lenalidomide
Starting dose	25mg
Dose level -1	20mg
Dose level -2	15mg
Dose level -3	10mg
Dose level -4	5mg
Dose level -5	Discontinue

Table 2: Dose Reduction based on 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.

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 Impairment:

Table 4: Dose modification of Bortezomib and Lenalidomide in Renal Impairment

Drug	Dose modification	
Bortezomib[a]	No dose adjustment is needed. Haemodialysis: No dose adjustment is needed, administer after haemodialysis.	
Lenalidomide[b]	**CrCl mL/min**	**Dose modification**
	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]Renal dose modifications from Giraud et al 2023 [b]Renal dose modifications from SmPC		

Hepatic impairment:

Table 5: Dose modification of Bortezomib and Lenalidomide in Hepatic Impairment

Drug	Grade *	Bilirubin Level	SGOT (AST) levels	Modification of starting dose
Bortezomib[a]	Mild	≤1 x ULN	> ULN	None
		>1 - 1.5 x ULN	Any	None
	Moderate	>1.5 - 3 x ULN	Any	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.
	Severe	> 3 x ULN	Any	
Lenalidomide[b]	No need for dose adjustment is expected.			
[a]Dose modifications from SmPC [b]Dose modifications from Giraud et al 2023				

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

Neuropathic pain and/or peripheral neuropathy:

Table 6: 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 7: 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 - Available on the NCCP website

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

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
- Patients on lenalidomide should be on prophylactic antithrombotic medicines. Aspirin is sufficient in patients with no 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. Consider use of Cholestyramine 4g OD in patients with lenalidomide-associated diarrhoea.
- Prophylactic laxatives to prevent lenalidomide induced constipation **(Refer to local policy)**
- 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**)
- Male patients must use condoms during treatment, during dose interruption and for at least 7 days following discontinuation of treatment 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

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

Bortezomib

- **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.

Lenalidomide

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

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

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Version	Date	Amendment	Approved By
1	05/04/2017		Dr Patrick Hayden Dr John Quinn
2	19/06/2019	Updated recommendation on Hep B reactivation and supportive care	Dr Patrick Hayden Dr John Quinn
3	01/11/2021	Reviewed. Amended treatment table. Updated exclusion criteria. Updated emetogenic potential and adverse effects.	Dr Patrick Hayden Dr John Quinn
3a	13/02/2024	Updated company support resources/ useful links section in line with NCCP standardisation.	NCCP
4	24/02/2025	Updated wording in indications. Updated exclusions section. Updated baseline tests section. Updated Tables 2, 3 and 6 and 7. Updated renal and hepatic dose modifications tables. Updated supportive care section. Updated regimen in line with NCCP standardisation.	Dr Patrick Hayden

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of bortezomib® 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