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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of newly diagnosed myeloma in adult patients with high risk features	C90	00416a	
Treatment of relapsed or refractory myeloma that has received prior therapy in adult patients with high risk features	C90	00416b	

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,b]Bortezomib	1.3mg/m^2	[c,d]SC (abdomen or thigh)	Every 21 days for up to 8 cycles
1-14 inclusive	Lenalidomide	25mg once daily	[e]PO	Every 21 days for up to 8 cycles
1,8 and 15	Dexamethasone	40mg once daily	[f]PO	Every 21 days for up to 8 cycles

[a] At least 72 hours should elapse between consecutive doses of bortezomib.

[b] 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.

[c] 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.

[d] 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.

[e] 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.

[f] Dexamethasone to be taken in the morning with food.

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, lenalidomide, dexamethasone or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
- Women of childbearing potential unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met
- 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
- 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 and day 8 each cycle
- Renal, liver and bone profile
- Blood pressure
- Pregnancy test every 28 days if female of childbearing potential
- 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.
- 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 of Lenalidomide Based on Thrombocytopenia

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

Table 3: Dose Reduction of Lenalidomide Based on Neutropenia

Neutrophils	Action
1st fall to < 0.5 x 10^9/L Return to ≥ 0.5 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 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	It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20ml/min). Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure.	
Lenalidomide	**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.		

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	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	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations			

*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 (asymptomatic; loss of deep tendon reflexes or paraesthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce dose to 1 mg/m^2 *or* Change treatment schedule to 1.3mg/m^2 once every week
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; clinical or diagnostic observations only 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

Adverse reactions	Recommended dose modification
Grade 4 Haematological toxicity (ANC < 0.5 x10^9/L)	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at a 25% reduced dose (1.3mg/m^2 reduced to 1mg/m^2; 1mg/m^2 reduced to 0.7mg/m^2). 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.
Grade 3 Non-haematological toxicity	
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.
Skin rash	Withhold treatment and evaluate clinically. If allergic reaction do not resume treatment.
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.
Angioedema	Discontinue treatment.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue treatment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Bortezomib: Low **(Refer to local policy)**
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
- 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 / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Bortezomib

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.
- **Gastrointestinal toxicity**: Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment.
- **Hepatic Impairment:** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.
- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is $<25 \times 10^9$/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.

- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
- **Renal Impairment:** Patients with renal impairment should be monitored closely.
- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).
- **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.

- **Teratogenetic 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), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) 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.
- **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:

- Additive hypotensive effect with anti-hypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of anti-hypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetics.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- 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:

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	Updates to new template 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

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