Bortezomib, Thalidomide and Dexamethasone (VTD) Induction Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Bortezomib, thalidomide and dexamethasone for induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation	C90	00274a	Bortezomib: Hospital Thalidomide: 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.

Bortezomib is administered twice weekly for two weeks on days 1 ,4, 8 and 11, dexamethasone on days 1-4 and 9-12 and thalidomide daily in a 21 day treatment cycle for four treatment cycles prior to ASCT or until disease progression or unacceptable toxicity occurs.
It is recommended that patients with at least partial response receive 2 additional cycles.

Day	Drug	Dose	Route	Cycle
1, 4, 8 and 11	Bortezomib	1.3mg/m^2	[a,b] SC (abdomen or thigh)	Every 21 days for up to 4 cycles[c]
1, 2, 3 ,4, 9,10,11,12	Dexamethasone	40mg once daily	PO	Every 21 days for up to 4 cycles[c]
1-21	Thalidomide	100mg[d]	PO	Every 21 days for up to 4 cycles[c]
[a]Note: 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				
[b]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 intravenous injection is recommended. At least 72 hours should elapse between consecutive doses of bortezomib. 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] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles				
[d]Patients may be started at a dose of thalidomide 50mg at the discretion of the prescribing consultant				

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron, thalidomide or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
- Women of childbearing potential unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met

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.
- Assessment and registration as per Thalidomide Pregnancy Prevention Program for both male and female patients.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV
  ***(Reference Adverse Events/Regimen Specific Complications for information on 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 prior to each cycle.
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)
- Pregnancy test every 28 days if female of childbearing potential.

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

Table 1: Dose reduction steps for bortezomib

Dose Level	Dose
Starting dose	1.3mg/m^2
Dose level 1	1.0mg/m^2
Dose level 2	0.7mg/m^2
Dose level 3	Discontinue

Haematological:

Table 2: Dose modification of bortezomib for haematological toxicity

Drug	ANC (x10^9/L)		Platelets (x10^9/L)	Dose Modification
Bortezomib	<0.5	Or	<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

Renal and Hepatic impairment:

Table 3: Dose modifications in patients with renal or hepatic impairment

Drug	Renal Impairment	Grade of Hepatic Impairment*	Bilirubin Level	SGOT (AST) levels	Modification of starting dose
Bortezomib	It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairmentnot undergoing dialysis (CrCL < 20ml/min).Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure	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	
Thalidomide	No specific dose recommendations	No specific dose recommendations. Monitor patients with severe hepatic impairment closely for adverse reactions			

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

Neuropathic pain and/or peripheral neuropathy:

Table 4: Recommended dose modifications for neuropathy

Drug	Severity of neuropathy*	Dose Modification
Bortezomib	Grade 1(asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
	Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))	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 (severe symptoms; limiting self care ADL)	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 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue treatment
Thalidomide	Grade 2	Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.
	Grade 3 or 4	Discontinue treatment

* Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

Dose reductions for other toxicities:

Table 5: Dose modification schedule based on adverse events

Drug	Adverse reactions*	Recommended dose modification
Bortezomib	Grade ≥3 Non-haematological toxicity	Withhold bortezomib until symptoms resolved to Grade 1 or baseline then reinitiate with one dose level reduction from 1.3mg/m^2 to 1 mg/m^2 or from 1mg/m^2 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.
	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 bortezomib
Thalidomide	Angioedema,	Discontinue thalidomide
	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, thalidomide treatment may be restarted at the original dose dependant on a benefit/risk assessment. Anticoagulant therapy should be continued during the course of thalidomide treatment.

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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

OTHER SUPPORTIVE CARE:

- 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).**
- Antiviral prophylaxis **(Refer to local policy).**
- Consider PJP prophylaxis **(Refer to local policy).**
- Prophylactic laxatives to prevent thalidomide induced constipation**(Refer to local policy).**
- Thromboprophylaxis **(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.

- **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.

Bortezomib

- **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 < 25,000/microliter. 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.
- **Progressive multifocal leukoencephalopathy (PML):** Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PM is suspected patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **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.
- **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.
- **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.
- **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.
- **Gastrointestinal toxicity:** Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment

Thalidomide

- **Teratogenetic effects:** Thalidomide must never be used by women who are pregnancy or by women who could become pregnant unless all the conditions of the Thalidomide Pregnancy Prevention Programme are met. These conditions must be fulfilled for all male and female patients.
- **Venous and arterial thromboembolic events:** There is an increased risk of venous and arterial

thromboembolism in patients treated with thalidomide particularly during the first 5 months of therapy. Previous history of thromboembolic events may also increase thromboembolic risk in these patients. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.

- **Allergic reactions and severe skin reactions**: Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of Thalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide must be discontinued for angioedema, anaphylactic reaction, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.
- **Somnolence:** Patients should be monitored and dose reduction may be required.

DRUG INTERACTIONS:

- Additive hypotensive effect with antihypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics
- 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.
- Thalidomide may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 anti-histamines, opiate derivatives, barbiturates and alcohol.
- Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmcodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	08/08/2016		Dr John Quinn
2	12/10/2018	Updated with new regimen template. Updated with Hepatitis B recommendations and dose modifications for thalidomide for peripheral neuropathy as per SmPC	Dr John Quinn
3	03/03/2021	Regimen review Updated advice regarding management of hepatitis B reactivation Addition of dose reduction steps for bortezomib Updated emetogenic potential Updated adverse events/regimen specific complications with regards to gastrointestinal toxicity for bortezomib and skin rash management for thalidomide as per SmPC update.	Dr John Quinn

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