Pomalidomide, Bortezomib and dexAMETHasone (PVD) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Pomalidomide in combination with bortezomib and dexAMETHasone for the treatment of adult patients with multiple myeloma who have received at least one prior treatment including lenalidomide	C90	00601a	Pomalidomide: CDS 01/12/2022 Bortezomib: 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 patient's individual clinical circumstances.

- Pomalidomide is administered daily for 2 weeks (14 days) followed by a 1 week (7 day) rest period as shown in table 1
- In cycle 1-8 bortezomib is administered twice weekly on day 1, 4, 8 and 11, dexAMETHasone is administered for two days each week on day 1, 2, 4, 5, 8, 9, 11 and 12 every 21 days
- From cycle 9 onwards bortezomib is administered once weekly on day 1 and 8 and dexAMETHasone is administered for two days each week on day 1, 2, 8, 9 every 21 days
- Each 21-day period is considered one treatment cycle.
- Treatment may be continued until disease progression or unacceptable toxicity occurs.

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

Table 1: Recommended administration of pomalidomide, bortezomib and dexAMETHasone

Cycle 1-8

Day	Drug	Dose	Route	Cycle Frequency
1-14	Pomalidomide	4 mg once daily	PO [a]in the evening may be preferred	Every 21 days
1, 4, 8, 11	[b]Bortezomib	1.3mg/m^2	[c,d,e] SC (abdomen or thigh)	Every 21 days
1, 2, 4, 5, 8, 9, 11 and 12	dexAMETHasone	[f]20 mg once daily	PO with food in the morning	Every 21 days

Cycle 9 onwards

Day	Drug	Dose	Route	Cycle Frequency
1-14	Pomalidomide	4 mg once daily	PO[a] in the evening may be preferred	Every 21 days
1 and 8	Bortezomib	1.3mg/m^2	[c,d,e] SC (abdomen or thigh)	Every 21 days
1, 2, 8 and 9	Dexamethasone	[f]20mg once daily	PO with food in the morning	Every 21 days

[a]Pomalidomide capsules should be taken at about the same time each day.
The capsules should not be opened, broken or chewed.
The capsules should be swallowed whole, preferably with water, either with or without food.
If the patient forgets to take a dose of pomalidomide on one day, then the patient should take the normal prescribed dose as scheduled on the next day. Patients should not adjust the dose to make up for a missing dose on previous days.

[b]For cycles 1-8, consideration may be given to use of bortezomib 1.3mg/m^2 once weekly in patients who experienced neuropathy previously or those with pre-existing neuropathy.

[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^o 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.

[e]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

[f]For patients >75 years of age, the dose of dexamethasone is 10 mg once daily

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

Table 2: Dosing schedule

Cycle 1-8 (21 day treatment cycle)																					
Drug	Week 1							Week 2							Week 3						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Bortezomib	✓			✓				✓			✓										
dexAMETHasone	✓	✓		✓	✓			✓	✓		✓	✓									
Cycle 9 onwards (21 day treatment cycle)																					
Drug	**Week 1**							**Week 2**							**Week 3**						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Bortezomib	✓							✓													
dexAMETHasone	✓	✓						✓	✓												

ELIGIBILITY:

- Indication as above
- ECOG performance status 0-2
- Refractory to lenalidomide
- 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.

CAUTION:

- Cardiac disease or risk factors

EXCLUSIONS:

- Hypersensitivity to pomalidomide, thalidomide, lenalidomide, bortezomib, boron, dexAMETHasone or any of the excipients
- Pregnancy
- Patients who are unable to comply with the Pomalidomide Pregnancy Prevention Programme
- Acute diffuse infiltrative pulmonary and pericardial disease

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)**
- Clinical 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

***(Reference Regimen Specific Complications for information on Hepatitis B reactivation)**

Regular tests:

- FBC; monitor platelet count at a minimum of day 1 and consider day 11 each cycle
- Monthly renal and liver profile, regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and thereafter as clinically indicated.
- Blood pressure, blood glucose (if being treated with oral hypoglycaemics)
- Urine pregnancy testing or serum hCG test every 28 days for women of childbearing potential as per Pregnancy Prevention Programme
- Assessment of peripheral neuropathy status
- Consider monitoring thyroid function tests

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:

- In older people, no dose adjustment is required for pomalidomide.
- For patients >75 years of age, the starting dose of dexAMETHasone is 10 mg once daily
- Pomalidomide and bortezomib therapy may be delayed independently of each other and dosing may continue with either component but consideration should be given to the timings of further treatment.
- In case of permanent discontinuation of any component of the treatment regimen, continuation of the remaining components is at the discretion of the prescribing consultant.
- Any dose modification should be discussed with a Consultant.

Table 3: Recommended dose reduction levels

Drug	Starting dose	Dose level -1	Dose level -2	Dose level -3
Pomalidomide	4mg	3mg	2mg	1mg[a]
Bortezomib	1.3mg/m^2	1.0mg/m^2	0.7mg/m^2	Discontinue
dexAMETHasone[b] (≤ 75 years)	20 mg	12 mg	8 mg	
dexAMETHasone[b] (> 75 years)	10 mg	6 mg	4 mg	
[a]If adverse reactions occur after dose reductions to 1 mg, then pomalidomide should be discontinued				
[b]If recovery from toxicities is prolonged beyond 14 days, then the dose of dexAMETHasone will be decreased by one dose level.				

Haematological:

Table 4: Recommended dose modifications for pomalidomide and bortezomib based on adverse reactions.

Drug	ANC (x10^9/L)		Platelets (x10^9/L)	Dose modification
Pomalidomide*	< 0.5 Or Febrile neutropenia (fever ≥ 38.5^{0}C and ANC < 1)	Or	< 25	Interrupt pomalidomide therapy, follow FBC weekly.
	ANC return to ≥ 1	Or	Return to ≥ 50	Resume pomalidomide treatment at one dose level lower than previous dose.
	For each subsequent drop < 0.5	Or	For each subsequent drop < 25	Interrupt pomalidomide treatment.
	ANC return to ≥ 1.0	Or	Return to ≥ 50	Resume pomalidomide treatment at one dose level lower than previous dose.
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.
*To initiate a new cycle of pomalidomide, the neutrophil count must be >1 x 10^9/L and the platelet count must be ≥ 50 x 10^9/L. In case of neutropenia; the physician should consider the use of growth factors.				

Renal and Hepatic Impairment:

Table 5: Recommended dose modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
	CrCl mL/min	Dose	Level	Dose		
Pomalidomide [a]	≥ 30	No dose adjustment is needed	Child-Pugh A/B	75% of the original dose		
	< 30	75% of the original dose	Child-Pugh C	50% of the original dose		
	Haemodialysis	75% of the original dose. Take dose following Haemodialysis.				
Bortezomib [b]	Renal impairment: No dose adjustment is needed. Haemodialysis: No dose adjustment is needed, administer after haemodialysis.		**Grade of Hepatic Impairment**	**Bilirubin Level**	**SGOT (AST) levels**	**Modification of starting dose**
			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	

[a] Pomalidomide (renal and hepatic - Giraud et al 2023)
[b] Bortezomib (renal - Giraud et al 2023; hepatic - SPC)

Management of adverse events:

Table 6: Dose Modification for Adverse Events

Drug	Adverse reactions*	Recommended dose modification
dexAMETHasone	**Dyspepsia** Grade 1-2 Grade ≥ 3	Maintain dose and treat with histamine (H2) blockers or Proton Pump Inhibitor (PPI). Decrease by one dose level if symptoms persist. Interrupt dose until symptoms are controlled. Add H2 blocker or PPI and decrease one dose level when dose restarted.
	Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
	Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
	Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
	Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed.
	Acute pancreatitis	Discontinue dexAMETHasone from treatment regimen.
	Other ≥ Grade 3 dexAMETHasone-related adverse events	Stop dexAMETHasone until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.
Pomalidomide	**Rash** Grade 2-3 Grade 4 or blistering (including angioedema, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected)	Consider dose interruption or discontinuation of pomalidomide treatment. Permanently discontinue treatment.
	Other Grade ≥ 3 adverse reactions	Interrupt pomalidomide treatment for remainder of cycle. Resume at one dose level lower than previous dose at next cycle (adverse event must be resolved or improved to ≤ Grade 2 before restarting).
Bortezomib	**Grade ≥ 3 Non-haematological toxicity (excluding neuropathy – see Table 7)**	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 bortezomib

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

Neuropathic pain and/or peripheral neuropathy:

Table 7: Recommended 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 1mg/m^2 or Change treatment schedule to 1.3mg/m^2 once per 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 per 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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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

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)**
- Prophylactic laxatives to prevent pomalidomide induced constipation **(Refer to local policy).**
- 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).**

- Prophylaxis for hepatitis B reactivation where hepatitis B screening is positive **(Refer to local policy).**
- Pomalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, depressed level of consciousness, confusion and dizziness have been reported with the use of pomalidomide. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with pomalidomide.
- Low dose antiviral prophylaxis (**Refer to local policy**).
- Consider PJP prophylaxis (**Refer to local policy**).

ADVERSE EFFECTS

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

REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation**: Hepatitis B virus status should be established before initiating treatment with pomalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when using pomalidomide in combination with dexAMETHasone in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. Previously infected patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

DRUG INTERACTIONS:

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

Company support resources/Useful links

Pomalidomide

- 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. Richardson et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20: 781–94
2. HPRA Safety Notice: Pomalidomide (Imnovid®): New important advice - hepatitis B virus status to be established before initiating treatment with pomalidomide. Available at https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---imnovid-(pomalidomide).pdf?sfvrsn=0
3. HPRA Safety Notice: Pomalidomide (Imnovid®): New important advice to minimise the risk of serious hepatotoxicity, interstitial lung disease and cardiac failure. Available at https://www.hpra.ie/docs/default-source/3rd-party-documents/dhpc-letter-imnovid-april-2015.pdf?sfvrsn=2

4. 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/
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7. Bortezomib (Velcade®) Summary of Product Characteristics. Accessed 26.01.2024. Last updated 04.06.2021. Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf
8. dexAMETHasone Summary of Product Characteristics. Accessed 26.01.2024. Last updated 24.06.2022. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1691-014-001_24062022144441.pdf

Version	Date	Amendment	Approved By
1	01/12/2022		Dr Janusz Krawczyk
2	18/07/2024	Reviewed. Updated treatment text. Updated baseline and regular tests. Caution section – inclusion of cardiac risk Updated pomalidomide (renal and hepatic) and bortezomib (renal only) to Giraud et al (2023). Updated Table 7 to align with SPC. Updated Other Supportive Care. Updated Adverse Effects / Regimen Specific Complications and drug interactions section as per NCCP standardisation. Added Company support resources / useful links section.	Dr Janusz Krawczyk

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.