Pomalidomide, Bortezomib and Dexamethasone (PVD) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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: Hospital

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, 4, 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.

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 [1]in the evening may be preferred	Every 21 days
1, 4 ,8, 11	[2]Bortezomib	1.3mg/m^2	[3,4,5] SC (abdomen or thigh)	Every 21 days
1,2,4,5,8,9,11 and 12	Dexamethasone	[6]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 [1]in the evening may be preferred	Every 21 days
1 and 8	Bortezomib	1.3mg/m^2	[3,4,5] SC (abdomen or thigh)	Every 21 days
1,2,8 and 9	Dexamethasone	[6]20mg once daily	PO with food in the morning	Every 21 days

[1]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.

[2]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).

[3] 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.

[4]The solution should be injected subcutaneously, at a 45-90° 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.

[5]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

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

Table 2: Dosing schedule

Drug	Cycle 1-8 (21 day treatment cycle)																				
	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	✓	✓		✓	✓			✓	✓		✓	✓									
Drug	**Cycle 9 onward (21 day treatment cycle)**																				
	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

EXCLUSIONS:

- Hypersensitivity to pomalidomide, bortezomib, boron, dexamethasone or any of the excipients
- Pregnancy
- Women of childbearing potential unless all the conditions of the pomalidomide Pregnancy Prevention Programme are met
- All patients unable to follow or comply with the required contraceptive measures
- 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
- Blood pressure, blood glucose (if patients on oral hypoglycaemics)
- Clinical assessment of peripheral neuropathy status
- VTE risk assessment
- Pregnancy test in women of childbearing age or evidence of a hysterectomy
- 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 Adverse Events/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)
- Pregnancy testing in females of childbearing potential as per Pregnancy Prevention Programme
- Assessment of peripheral neuropathy status

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. Any dose modification should be discussed with a Consultant.
- 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 old)	20 mg	12 mg	8 mg	
Dexamethasone[b] (>75 years old)	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 x 10^9/L	Or	Return to ≥ 50 x 10^9/L	Resume pomalidomide treatment at one dose level lower than previous dose
	For each subsequent drop < 0.5 x 10^9/L	Or	For each subsequent drop < 25 x 10^9/L	Interrupt pomalidomide treatment
	ANC return to ≥ 1.0 x 10^9/L	Or	Return to ≥ 50 x 10^9/L	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			
Pomalidomide	No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take their pomalidomide dose following haemodialysis.	Patients with serum total bilirubin > 1.5 x ULN (upper limit of normal range) were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide. No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.			
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	**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	

Management of adverse events:

Table 6: Dose Modification for Adverse Events

Drug	Adverse reactions*	Recommended dose modification
Dexamethasone	**Dyspepsia** Grade 1-2	Maintain dose and treat with histamine (H2) blockers or Proton Pump Inhibitor (PPI). Decrease by one dose level if symptoms persist
	Grade ≥ 3	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 patient from dexamethasone 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**	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	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; 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*	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- In case of neutropenia, the consultant may consider the use of growth factors in patient management.
- Thromboprophylaxis - All patients should receive aspirin unless contraindicated. Patients deemed to be at higher risk e.g. previous thromboembolic events should receive LMWH or 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 / REGIMEN SPECIFIC COMPLICATIONS

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

Pomalidomide is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

- **Haematological toxicity:** Patients should be monitored for haematological adverse events. A dose modification may be required (see table 4).
- **Peripheral neuropathy:** Patients with ongoing ≥Grade 2 peripheral neuropathy were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide. Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

Pomalidomide

- **Teratogenetic effects**: Pomalidomide 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 Pregnancy Prevention Programme are met.
- **Thromboembolic events**: Patients receiving pomalidomide in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise

all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia). Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Anti-coagulation therapy (unless contraindicated) is recommended, (such as acetylsalicylic acid, warfarin, heparin or clopidogrel), especially in patients with additional thrombotic risk factors. Erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution.

- **Thyroid disorders**: Cases of hypothyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.
- **Significant cardiac dysfunction**: Patients with significant cardiac dysfunction, (CHF, myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide. Cardiac failure events, including congestive heart failure and pulmonary oedema have been reported, mainly in patients with pre-existing cardiac disease or risk factors. Pomalidomide should be used with caution in patients with cardiac disease or risk factors and if used, patients should be monitored for signs or symptoms of cardiac failure.
- **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.
- **Second primary malignancies:** Second primary malignancies such as non-melanoma skin cancer, have been reported in patients receiving pomalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.
- **Allergic reaction**: Angioedema, anaphylactic reaction and severe dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued permanently for angioedema, Grade 4 rash, exfoliative or bullous rash or if SJS, TEN or DRESS is suspected.
- **Dizziness and confusion**: Dizziness and confusional state have been reported with pomalidomide. Patients must avoid situations where dizziness or confusion may be a problem and not to take other medicinal products that may cause dizziness or confusion without first seeking medical advice.
- **Interstitial lung disease (ILD)**: ILD and related events have been observed with pomalidomide. Patients with an acute onset or unexplained worsening of pulmonary **symptoms should be care**fully assessed to exclude ILD. Treatment with pomalidomide should be interrupted pending investigation of these symptoms. If ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and risks.
- **Hepatotoxicity**: Markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with pomalidomide. Serious cases of acute hepatitis due to pomalidomide have occurred that led to hospitalisation and discontinuation of treatment. Regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and thereafter as clinically indicated.
- **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.

Bortezomib

- **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.
- **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.
- **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.

Dexamethasone

- **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).

DRUG INTERACTIONS:

- If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.
- 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-diabetic medications.
- 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.
- Current drug interaction databases should be consulted for more information.

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. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
5. Pomalidomide (Imnovid®) Summary of Product Characteristics Accessed Dec 2022. Available at https://www.ema.europa.eu/en/documents/product-information/imnovid-epar-product-information_en.pdf
6. Bortezomib (Velcade®) Summary of Product Characteristics. Accessed Dec 2022. Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/12/2022		Dr Janusz Krawczyk

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.