Pomalidomide and Dexamethasone Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment in combination with dexamethasone of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including with both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy	C90	00245a	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.

Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma.

Pomalidomide is administered daily for 3 weeks (21 days) followed by a 1week (7 day) rest period (total 28 day cycle). Treatment is administered continuously or until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route	Cycle
1-21 (no treatment on days 22-28)	Pomalidomide	4 mg/day	PO [1]in the evening may be preferred	Every 28 days
1,8,15 and 22	Dexamethasone	[2]40 mg/day	PO with food in the morning	Every 28 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 patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.				

ELIGIBILITY:

- Indications as above
- Life expectancy > 3 months
- ECOG performance status 0-2

EXCLUSIONS:

- Hypersensitivity to pomalidomide, thalidomide, lenalidomide or any of the excipients
- Pregnancy
- Women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met
- Male patients unable to follow or comply with the required contraceptive measures

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),
- 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 every week for first 8 weeks of treatment and then monthly.
- 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)
- Consider pregnancy testing in females 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:

- In older people, no dose adjustment is required for pomalidomide.
- For patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
- Any dose modification should be discussed with a Consultant.

Table 1: Recommended dose reduction levels

Drug	Starting dose	Dose level -1	Dose level -2	Dose level -3
Pomalidomide	4mg	3mg	2mg	1mg*
Dexamethasone** (≤75 years)	40 mg	20 mg	10 mg	
Dexamethasone** (>75 years)	20 mg	12 mg	8 mg	
*If adverse reactions occur after dose reductions to 1 mg, then pomalidomide should be discontinued				
**If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.				

Haematological:

Table 2: Pomalidomide dose modification based on adverse reactions.

Toxicity	Dose modification
***Neutropenia** ANC< 0.5 x 10^9/L or Febrile neutropenia (fever ≥ 38.5^{0}C and ANC < 1 x 10^9/L)	Interrupt pomalidomide therapy, follow FBC weekly
ANC return to ≥ 1 x 10^9/L	Resume pomalidomide treatment at 3mg daily
For each subsequent drop < 0.5 x 10^9/L	Interrupt pomalidomide treatment
ANC return to ≥ 1.0 x 10^9/L	Resume pomalidomide treatment at 1mg less than the previous dose.
***Thrombocytopenia** Platelets < 25 x10^9/L	Interrupt pomalidomide therapy, follow FBC weekly
Platelets return to ≥ 50 x 10^9/L	Resume pomalidomide treatment at 3mg daily
For each subsequent drop < 25 x 10^9/L	Interrupt pomalidomide treatment
Platelets return to ≥ 50 x 10^9/L	Resume pomalidomide treatment at 1mg less than the previous dose.
*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 3: Dose modifications in renal and hepatic impairment

Renal impairment	Hepatic impairment
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.

Management of adverse events:

Table 4: 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 ≥ 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	Consider dose interruption or discontinuation of pomalidomide treatment.
	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)	Permanently discontinue treatment
	Other Grade ≥ 3 adverse reactions	Interrupt pomalidomide therapy. Treatment with pomalidomide may be restarted at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion. If adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pomalidomide: Minimal to 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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

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

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

- **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.
- **Haematological events**: Neutropenia was the most frequently reported Grade 3 or 4 haematological adverse reaction in patients with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Patients should be monitored for haematological adverse reactions, especially neutropenia. Patients should be advised to report febrile episodes promptly. A dose modification may be required (see Table 1). Patients may require use of blood product support and /or growth factors.
- **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.
- **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.
- **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 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**: Reactivation of hepatitis B has been reported rarely following treatment with pomalidomide plus dexamethasone in patients previously infected with the hepatitis B virus. Some of these cases have progressed to acute hepatic failure and resulted in discontinuation of pomalidomide. 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:

- If strong inhibitors of CYP1A2 (e.g. ciprofloxacin) are co-administered with pomalidomide, patients should be closely monitored for the occurrence of adverse reactions.
- Current drug interaction databases should be consulted for more 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:

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2. Lacy MQ, Hayman SR et al. Pomalidomide (CC4047) Plus Low-Dose Dexamethasone As Therapy for Relapsed Multiple Myeloma. J Clin Oncol 2009;27:5008-14
3. Guidelines for the Diagnosis and Management of Multiple Myeloma 2013 http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_updated_29_aug_RG_jzw_(3).pdf
4. 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
5. Imnovid®Summary of Product Characteristics Accessed October 2020. Available at https://www.ema.europa.eu/en/documents/product-information/imnovid-epar-product-information_en.pdf
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. 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

Version	Date	Amendment	Approved By
1	01/02/2016		Dr Patrick Hayden
2	12/09/2016	Updated to include information on Hepatitis B reactivation as per safety update from HPRA. Updated information on dosing in renal and hepatic impairment and information on secondary primary malignancies under Adverse Events as per SmPC	Dr Patrick Hayden
3	15/10/2018	Updated with new NCCP regimen template. Updated allergic reactions in adverse events as per SmPC	Dr Patrick Hayden
4	10/03/2021	Amended treatment table to clarify dexamethasone dosage Updated baseline test recommended dose modification in hepatic impairment as per SmPC update	Dr Patrick Hayden

		Updated management of adverse events section with regard to rashes as per SmPC update Updated emetogenic potential	
4a	13/02/2024	Added COMPANY SUPPORT RESOURCES/Useful Links section	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.