Pomalidomide and low dose dexamethasone

Indication

Treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

(NICE TA 427)

ICD-10

Codes with a pre-fix C90.

Regimen details

Day	Drug	Dose	Route
1 - 21	Pomalidomide	4 mg OD	PO
1, 8, 15 and 22	Dexamethasone	40 mg OM*	PO

* 20 mg OM for patients aged > 75 years

Cycle frequency

28 days

Number of cycles

Continue until disease progression (e.g. International Myeloma Working Group (IMWG) criteria) or unacceptable toxicity.

Administration

Pomalidomide is available as 1mg, 2mg, 3mg and 4mg capsules.

Pomalidomide should be swallowed whole with water, either with or without food, at the same time each day. The capsules should not be broken, opened or chewed. Patients should be advised to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

Pomalidomide must be prescribed and dispensed in accordance with the pregnancy prevention programme. Prescription authorisation is required for each dispensing. In line with the conditions of the Pregnancy Prevention Programme - dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of 4 weeks, and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetogenic potential. Routine antiemetics are not usually required.

Additional supportive medication

Thromboprophylaxis is required unless contraindicated. Aspirin is appropriate for patients who have no additional risk factors. For patients with additional thromboembolic risk factors (such as immobility, dexamethasone >20mg/day) a low molecular weight heparin is recommended for the first 4 cycles. It may then be appropriate to switch to aspirin.

H_2 antagonist or proton pump inhibitor

Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only

Bisphosphonates as per local policy

Antifungal, antiviral and PCP prophylaxis as per local policy

Extravasation

N/A

Investigations – pre cycle 1

Investigation	Validity period
FBC and clotting screen	Baseline – results valid for 7 days
U+Es (including creatinine)	Baseline – results valid for 7 days
LFTs	Baseline – results valid for 7 days
Calcium	Baseline – results valid for 7 days
Urine pregnancy test (women of childbearing potential)	3 days Prescription dispensed within 7 days of the pregnancy test*
Viral screening – HIV, hepatitis B and C	14 days

*Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day

Pomalidomide is contraindicated in women of childbearing potential, unless all the conditions of the pregnancy prevention programme are met and in men unable to follow or comply with the required contraceptive measures.

Consider baseline cardiac and respiratory assessment as per MHRA alert:

Cardiac failure/interstitial lung disease/ hepatotoxicity:

- Use with caution in cardiac disease or those with cardiac risk factors. Monitor for signs and symptoms of cardiac failure.
- If patient reports acute or worsening respiratory symptoms, stop pomalidomide and assess promptly to exclude/confirm interstitial lung disease. If confirmed assess risks and benefits of restarting treatment.
- Liver function must be regularly monitored, particularly during the first 6 months of treatment.

www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicityOther tests useful for staging, informing treatment and assessing response: serum calcium, albumin, uric acid, CRP, plasma viscosity, serum protein electrophoresis and immunofixation for quantitation of monoclonal protein and immunoglobulins, serum free light chain assay, β2 microglobulin, LDH, marrow myeloma FISH.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for the first 8 weeks, then monthly - valid for 72 hrs
U+Es (including creatinine)	Every 2 weeks for the first 8 weeks, then monthly - valid for 72 hrs
LFTs	Every 2 weeks for the first 8 weeks, then monthly - valid for 72 hrs
Calcium	Every 2 weeks for the first 8 weeks, then monthly - valid for 72 hrs
Pregnancy test (women of child bearing potential)	3 days Prescription dispensed within 7 days of the pregnancy test

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils*	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance	≥ 45mL/min
Bilirubin	< ULN

*Consider the use of G-CSF.

Dose modifications

- **Haematological toxicity**

Prior to commencing cycle: neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L

Thrombocytopenia

Platelets (x 10^9/L)	**Action**
< 25 (1st occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 50 x 10^9/L resume at 3mg OD
< 25 (2nd occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 50 x 10^9/L resume at 2mg OD
< 25 (3rd occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 50 x 10^9/L resume at 1mg OD

Neutropenia

Neutrophils (x 10^9/L)	**Action**
< 0.5 or febrile neutropenia (neutrophils <1.0 x 10^9/L + fever) (1st occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 1.0 x 10^9/L resume at 3mg OD
< 0.5 or febrile neutropenia (2nd occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 1.0 x 10^9/L resume at 2mg OD
< 0.5 or febrile neutropenia (3rd occurrence)	Withhold pomalidomide, monitor FBC weekly Once recovered to ≥ 1.0 x 10^9/L resume at 1mg OD

- **Renal impairment**

No dose adjustments are required for renal impairment. If a patient is on haemodialysis, on dialysis days the dose should be taken following dialysis.

- **Hepatic impairment**

Patients with raised bilirubin 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. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.

- **Other toxicities**

MHRA alert - Cardiac failure/interstitial lung disease/ hepatotoxicity:

If patient reports acute or worsening respiratory symptoms, stop pomalidomide and assess promptly to exclude/confirm interstitial lung disease. If confirmed assess risks and benefits of restarting treatment.

For any Grade 3 or 4 toxicities, stop treatment and restart treatment with a 1 mg dose reduction, when resolved to ≤ Grade 2 at the consultants' discretion.

If adverse reactions occur after dose reductions to 1 mg, discontinue pomalidomide.
Pomalidomide interruption or discontinuation should be considered for Grade 2-3 rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, and should not be resumed following discontinuation for these reactions.

Steroid side effects:
Dexamethasone dosing should be modified if necessary using the following dosing levels:

Age ≤ 75 years		**Dexamethasone dose**
	Starting dose	40mg OM on days 1, 8, 15 and 22
	Dose level -1	20mg OM on days 1, 8, 15 and 22
	Dose level -2	10mg OM on days 1, 8, 15 and 22
Age > 75 years		
	Starting dose	20mg OM on days 1, 8, 15 and 22
	Dose level -1	12mg OM on days 1, 8, 15 and 22
	Dose level -2	8mg OM on days 1, 8, 15 and 22

Dexamethasone dose modifications

Toxicity	**Grade**	**Dose Modification**
Dyspepsia	Grade 1-2	Maintain dose and treat with H_2 antagonist or equivalent. Reduce dose one level if symptoms persist.
	≥ Grade 3	Withhold until symptoms are controlled. Add H_2 antagonist or equivalent and resume with one dose level reduction.
Oedema	≥ Grade 3	Use diuretics as needed and continue with one dose level reduction.
Confusion or mood alteration	≥ Grade 2	Withhold until symptoms resolve. Resume with one dose level reduction.
Muscle weakness	≥ Grade 2	Withold until muscle weakness ≤ Grade 1. Resume with one dose level reduction.
Hyperglycaemia	≥ Grade 3	Reduce dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed.
Acute pancreatitis		Discontinue dexamethasone.
Other dexamethasone adverse events	≥ Grade 3	Withhold until resolved to ≤ Grade 2. Resume with one dose level reduction.

If recovery from dexamethasone toxicity is prolonged beyond 14 days, the dose should be reduced by one dose level.

Adverse effects - for full details consult product literature/ reference texts

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening birth defects and pomalidomide is teratogenic in animal studies.

Adverse reactions tend to occur more frequently within the first 2 cycles of treatment with pomalidomide.

- **Serious side effects**

Myelosuppression
Tumour lysis syndrome
Teratogenicity
Haemorrhage
Thromboembolic events
Peripheral neuropathy
Cardiotoxicity
Interstitial lung disease

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Peripheral neuropathy
Peripheral oedema
Sleep disturbance, psychosis (dexamethasone)
Hepatic dysfunction

- **Other side effects**

Dizziness
Confusion

Significant drug interactions – for full details consult product literature/ reference texts

If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide to 50%.

Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions due to P450 isoenzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters.

Additional comments

References

- Summary of Product Characteristics: Pomalidomide (Celgene) accessed 27 July 2016 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 427 accessed 18 Oct 2017 via www.nice.org.uk
- Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS™ (MM-010): a phase 3b study in refractory multiple myeloma. Meletios A. Dimopoulos, et al. Blood 2016: -2016-02-700872
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- Mark TM, Rodriguez M, Shah M, Quinn R, Campbell J, Abdullah R, Pearse RN, Zafar F, Pekle K, Mignott P, Jayabalan D, Ely SA, Coleman M, Chen-Kiang S, Niesvizky R. ClaPD (Clarithromycin/[Biaxin(R)], Pomalidomide, Dexamethasone) Therapy in Relapsed or Refractory Multiple Myeloma. ASH Annual Meeting Abstracts 2011 118: 635.
- MHRA drug alert (2015) Accessed 27 July 2016 via www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity

Written/reviewed by: Dr A Whiteway (Consultant Haematologist, North Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: October 2017