POMALIDOMIDE AND LOW DOSE DEXAMETHASONE

INDICATION

Multiple myeloma at third or subsequent relapse, i.e. after 3 previous treatments including both lenalidomide, bortezomib, as well as alkylators. [NICE TA427]. **Requires Blueteq approval**

Multiple myeloma at 1st relapse (i.e. after one prior line of therapy) or 2nd relapse (i.e. after two prior lines of therapy), in patients previously treated with lenalidomide, in order to reduce the need for chemotherapy and reduce admissions and risk of neutropenia. **COVID Blueteq approval is required.**

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
    - FBC & film
    - Clotting screen
    - U&Es
    - LFTs
    - Calcium
    - Albumin
    - Uric acid
    - CRP
    - Baseline random blood glucose level
    - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
    - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
    - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
    - Serum free light chain assay (Freelite)
    - β2 microglobulin
    - LDH
    - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
    - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
    - Group and save
    - Imaging as per NICE/network guidance and clinical presentation
    - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)
    - Formal assessment of performance status (WHO score)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations

- Plasma viscosity if hyperviscosity suspected

2. Fertility - all patients should be offered fertility advice, as appropriate.
3. Hydration - fluid intake of at least 3 litres /day should be attempted.
4. Document patient's height and weight, dose on actual body weight.
5. Document patient's performance status.
6. Treatment must be agreed at the relevant MDT.
7. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent for the treatment including signing Celgene Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE-ASSESSMENT

1. The conditions of the Pomalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of pomalidomide must be in line with the Pregnancy Prevention Programme.
2. Clinical Assessment of thrombo-embolic risk.
3. Consider baseline cardiac and respiratory assessment as per MHRA alert on risk of cardiac failure and interstitial lung disease.

DRUG REGIMEN / CYCLE FREQUENCY

Pomalidomide	4mg PO daily on days 1-21	Nocte
WITH		
Dexamethasone	40 mg PO daily for patients aged ≤ 75 years	D1, 8, 15, 22
OR		
Dexamethasone	20 mg PO daily for patients aged > 75 years	D1, 8, 15, 22

Consider adding clarithromycin 500 mg bd (250mg bd if not tolerating the full dose)
Dexamethasone should not be stopped (Unlike lenalidomide based therapy)

CYCLE FREQUENCY

Cycle repeats every 28 days and therapy can continue until progression or toxicity.

DOSE MODIFICATIONS

Dosing levels for pomalidomide:

Dose level	Daily pomalidomide dose
Starting dose	4mg
Level-1	3mg
Level-2	2mg
Level-3	1mg

Haematological

To initiate a new cycle of Pomalidomide, ANC ≥ 1.0 x 10^9/L and Platelets ≥ 50 x 10^9/L

Toxicity	Dose Modification
Neutropenia:	
ANC < 0.5 x 10^9/L OR Febrile Neutropenia and ANC < 1.0 x 10^9/L. When ANC return to ≥1 x 10^9/l	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at the next lower dose (e.g. if starting dose was 4mg, reduce to 3 mg OD)
For each subsequent drop ANC < 0.5 x 10^9/L When ANC ≥ 1.0 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose. (e.g. if previously reduced to 3mg, next dose level is 2mg daily)
Thrombocytopenia:	
Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at the next lower dose (e.g. if starting dose was 4mg, reduce to 3 mg OD)
For each subsequent drop Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose (e.g. if previously reduced to 3mg, next dose level is 2mg daily)

If toxicities occur after dose reductions to 1 mg daily, then discontinue pomalidomide.

Weekly injections of G-CSF can be administered to keep maintain dose intensity (aim to keep neutrophil counts >1.0)

Non-Haematological

Toxicity	Dose Modification
-Grade 3 or 4 -When resolved to Grade ≤ 2	-Interrupt Pomalidomide -Resume Pomalidomide at 1mg less than previous dose (e.g. if the current dose is 4mg, next dose level is 3mg daily)

If toxicities occur after dose reductions to 1 mg, then discontinue Pomalidomide.

Rash:

G2-3: Consider dose interruption or discontinuation of pomalidomide treatment.
G 4 or blistering (including angioedema, anaphylactic reaction, 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

Renal / Hepatic Impairment

Renal	Hepatic
- No dose adjustment required in renal impairment. -On haemodialysis days, patients should take pomalidomide following haemodialysis	Patients with serum total bilirubin > 1.5 x ULN 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.

INVESTIGATIONS - Pre-treatment and during

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC – consider weekly for first cycle then monthly
- U&E, Ca++, LFTs - monthly.
- Ig's, paraprotein, urinary BJP and serum free light chain levels in patients with light chain disease or non-secretory myeloma.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intoleranc

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Consider prophylactic fluconazole 50mg OD if appropriate
- Consider prophylactic co-trimoxazole 480mg to 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-3), at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function
- Proton pump inhibitor or H_2 antagonist at clinician's discretion.
- Thromboprophylaxis/anticoagulation see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3

Note: If a strong inhibitor of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) is co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

EMETIC RISK

Minimal.

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic:** The Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of pomalidomide must be in line with the pregnancy prevention programme.

- **Myelosuppression**: Very common, including neutropenia and thrombocytopenia which may require dose interruptions and reductions. Check bloods at least monthly. Monitor patients with neutropenia for signs of infection. Patients should be advised to monitor themselves for bleeding or bruising, especially if prophylactic VTE treatments are concomitantly administered. Follow dose modifications for haematological toxicity as per section above.

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with pomalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

  1. Prophylactic low-molecular weight heparin OR
  2. Prophylactic. apixaban 2.5mg bd (check product specific information)

  Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors.

If VTE occurs, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- Fatigue, dizziness and confusion
- Peripheral neuropathy, diarrhea/constipation, pneumonia, peripheral oedema.
- **Risks of cardiac failure, interstitial lung disease and hepatotoxicity**: There is a published MHRA drug alert (2015) on pomalidomide and risks of cardiac failure, interstitial lung disease and hepatotoxicity. See weblink: https://www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity.

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

1. Meletios A. et al. Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study. ASH Annual Meeting Abstracts 2012 120:LBA-6
2. Leleu X. et al, Intergroupe Francophone du Myélome. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide–refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. Blood. 2013 Mar 14;121(11):1968-75.
3. Miguel JS. et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066.
4. 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.
5. Imnovid® (Pomalidomide 4mg) eMC UK Summary of Product Characteristics for, Celgene, Mar 2022
6. NICE. Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England. 2020. Available at: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381 (last accessed: 12.06.2020)

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Indication, pre assessment, drug interaction, adverse effects, contraindications section removed	May 2016	1.3	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated indication, renal/hepatic impairment, concurrent medicines, drug interactions and references	July 2017	1.4	June 2018
Nadjoua Maouche (Haematology Pharmacist)	Standardise VTE information, pre-assessment, investigation, concurrent medication, adverse effects sections.	June 2018	1.5	June 2019
Myeloma Protocol Review 2019	Update of indications, concurrent medication, and references	June 2019	1.6	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Update with the new indication during COVID-19 pandemic	June 2020	1.7	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	1.8	June 2021
NSSG Myeloma Group	Annual myeloma protocol review 2022, updated: drug regimen, dose modification sections	June 2022	1.9	June 2023
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	2.0	June 2023