Thames Valley
Strategic Clinical Network

IXAZOMIB WITH LENALIDOMIDE AND DEXAMETHASONE

INDICATION

Relapsed multiple myeloma patients, who have received two or more prior lines of therapy and who were non-refractory to IMiD and to PI. This regimen is funded via **CDF interim Funding.** Requires **Blueteq approval**

The CDF criteria mandate that all 3 drugs in the combination (i.e. ixazomib, lenalidomide and dexamethasone) must be commenced at the same time and Ixazomib cannot be added in as an additional agent in the treatment of patients who have already previously commenced treatment with lenalidomide and dexamethasone.

Relapsed multiple myeloma patients, who have received one prior line of therapy and who were non-refractory to IMiD and to PI. **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
   - Thyroid function.
   - Baseline random blood glucose level
   - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
   - 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 before each cycle.
- Group and save
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine and immunophenotype if appropriate

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

Additional Investigations

1. 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. Treatment must be agreed at the relevant MDT.
6. Document patient's performance status
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-ASSESMENT

1. The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Lenalidomide Pregnancy Prevention Programme.
2. Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

Ixazomib	The starting dose is 4 mg orally once a week on days 1, 8, and 15
WITH	
Lenalidomide (continuous therapy)	The starting dose is 25 mg orally once daily on days 1 to 21
AND	
Dexamethasone	40 mg PO once a week on days 1, 8, 15 and 22 NB: a 20mg starting dose should be considered in the elderly or if steroid-related side effects develop

Note:
Ixazomib should be taken at least one hour before or at least two hours after food.
A delayed or missed ixazomib dose should not be taken within 72 hours of the next scheduled dose.

CYCLE FREQUENCY
Cycles repeat every 28 days (i.e. 3 weeks on lenalidomide then 1 week off) until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:
• Platelets ≥ 75 x 10^9/L and ANC ≥ 1.0 x 10^9/L.
• Non-haem toxicities should resolve to ≤G1 or baseline.
G-CSF and platelet support should be considered as appropriate

IXAZOMIB AND LENALIDOMIDE DOSE REDUCTION LEVELS
Ixazomib

starting dose	1st reduction level	2nd reduction level	
4 mg	3 mg	2.3mg	Discontinue

Lenalidomide

starting dose	1st reduction level	2nd reduction level	3rd reduction level
25mg	15mg	10mg	5mg

<u>Recommended dose adjustments due to treatment-related toxicities:</u>
For overlapping toxicities of thrombocytopenia, neutropenia and rash, use an alternating dose modification approach, with the first modification to reduce or withhold lenalidomide.
Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide and ixazomib.
Note: Consider re-escalating lenalidomide and/or ixazomib dose provided toxicities have completely resolved.
Thrombocytopenia:

When platelets	Recommended Course
First fall to < 30 x 10^9/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at its next lower dose and ixazomib at its most recent dose.
Second fall to < 30 x 10^9/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at its most recent dose, resume ixazomib at the next lower dose.
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 10^9/L	Alternate dose modification (reduction) of lenalidomide and ixazomib

Neutropenia:

When neutrophils	Recommended Course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide and ixazomib treatment. Administer G-CSF for 3 days and recheck FBC.
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at its next lower dose and ixazomib at its most recent dose.
Second fall to < 0.5 x 10^9/L	Interrupt lenalidomide and ixazomib treatment. Administer G-CSF for 3 days and check FBC
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at its most recent dose and ixazomib its next lower dose.
For each subsequent drop below < 0.5 x 10^9/L	Alternate dose modification of lenalidomide and ixazomib

Rash:

Grade	Recommended Course
2 or 3	**1st occurrence**: Withhold lenalidomide until rash recovers to ≤ Grade 1. Following recovery, resume lenalidomide at the next lower dose. **2nd occurrence**: If Grade 2 or 3 rash occurs again, withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose **For additional occurrences**, alternate dose modification (reduction) of lenalidomide and ixazomib
4	Discontinue treatment regimen

Peripheral Neuropathy:

Ixazomib:

Grade	Recommended Course
Grade 1 *(asymptomatic; loss of deep tendon reflexes or paresthesia)* with pain, **OR** Grade 2 *(moderate symptoms; limiting instrumental Activities of Daily Living (ADL)*	Withhold ixazomib until recovery to ≤Grade 1 without pain or baseline then resume at most recent dose.
Grade 2 with pain, **OR** Grade 3 *(severe symptoms; limiting self-care ADL***)*	Withhold ixazomib until recovers to ≤Grade 1 or baseline then resume at the next lower dose
Grade 4 *(life-threatening consequences; urgent intervention indicated),* **AND/OR** *severe autonomic neuropathy*	Discontinue treatment

Lenalidomide:

Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.

RENAL AND HEPATIC IMPAIRMENT:

Lenalidomide

Renal		Hepatic
30 > CrCl < 50 ml/min	10mg once daily*	No formal studies. No specific dose recommendations
CrCl < 30 ml/min, no dialysis	15 mg every other day**	
CrCl < 30 ml/min, requiring dialysis	5 mg once daily***	
*****Can increase to15mg OD if no response and patient tolerating ** Can increase to 10mg OD if no response and patient tolerating *** On dialysis day, administer dose after dialysis/		

Ixazomib

Renal	Hepatic
Reduce the starting dose to 3mg if severe renal impairment (CrCl < 30 ml/min) or end-stage renal disease requiring dialysis. Ixazomib is not dialysable and, therefore, can be administered without regard to the timing of dialysis	Reduce the starting dose to 3mg in moderate (total bilirubin >1.5-3 x ULN) or severe (total Bilirubin >3 x ULN) hepatic impairment.

INVESTIGATIONS

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, LFTs, U&E, Ca++
- Ig's, paraprotein, urinary BJP where present. Freelite assay may provide an early indication of response.
- Consider bone marrow assessment after 4 -6 cycles in patients with non secretory myeloma, or to confirm complete remission.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

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CONCURRENT MEDICATION

- 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)
- Prophylactic fluconazole 50mg OD if appropriate
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-3)
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Thromboprophylaxis/anticoagulation see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3

- Consider Loperamide 4mg stat then 2mg prn every 4 hours up to maximum of 16mg in 24 hours to start at the first episode of diarrhoea
- Consider cholestyramine if suspicion of bile salt malabsorption with lenalidomide
- Consider metoclopramide or cyclizine when required if nausea and/or vomiting experienced.

Avoid concomitant administration of ixazomib with strong CYP3A inducers (Such as rifampin, phenytoin, carbamazepine, and St. John's Wort). Closely monitor patients for disease control if co-administration with a strong CYP3A inducer cannot be avoided

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EMETIC RISK

Minimal emetic risk (also see concurrent meds section for anti-emetics). Nausea tends to be associated with Ixazomib administration, consider dose reduction of Ixazomib if uncontrolled nausea/vomiting. Consider maintaining steroid administration on the days of ixazomib dosing.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- **Myelosuppression**: including neutropenia and thrombocytopenia which may require dose interruptions and reductions. Monitor patients with neutropenia for signs of infection. Platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. 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.

- **Diarrhoea:** Diarrhea was reported in 42% of patients requiring use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small percentage of patients with lenalidomide, considers addition of cholestyramine.

- **Other Gastrointestinal Toxicities:** constipation, nausea, and vomiting, have been reported occasionally requiring use of antiemetic medications

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with lenalidomide. 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

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

- **Peripheral Neuropathy:** Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. Peripheral neutopathy mostly of grades 1 and 2 has been reported with up to 25% of patients. New or worsening peripheral neuropathy may require dose modification; see above dose modification section above.

- **Peripheral Edema:** Evaluate for underlying causes and provide supportive care, as necessary. Consider dose adjustments for dexamethasone. Adjust ixazomib for grade 3 or 4 symptoms.

- **Cutaneous Reactions:** The most common type of rash reported included maculopapular and macular rash. Manage rash with supportive care or with dose modification as above.

- **Hepatotoxicity:** Monitor liver function tests regularly and adjust dosing for Grade 3 or 4 symptoms.

- **There is an MHRA alert on an increased risk of secondary malignancies in three large trials of Lenalidomide treatment**. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum

- **Posterior reversible encephalopathy syndrome:** Posterior reversible encephalopathy syndrome (PRES) has occurred in patients receiving ixazomib. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, altered consciousness, and visual disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. In patients developing PRES, discontinue ixazomib

- Hypothyroidism has been reported in patients on lenalidomide. Baseline assessment of thyroid function and ongoing monitoring is recommended.

TREATMENT RELATED MORTALITY

4-6%

REFERENCES

1. Philippe Moreau*,1, Tamás Masszi, MD2, et al Oral Ixazomib, Lenalidomide and Dexamethasone (IRd), for Multiple Myeloma: The Phase 3 Tourmaline-MM1 Study (NCT01564537). N Engl J Med. 2016 Apr 28;374(17):1621-34
2. Revlimid ® 25mg eMC UK Summary of Product Characteristics for, Celgene, June 2020
3. NINLARLO® eMC UK Summary of Product Characteristics for, Takeda, October 2020

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, pre assessment, adverse effects, VTE and prescribing details removed	May 2016	1.1	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated Ixazomib in renal impairment, concurrent medication and references	July 2017	1.2	June 2018
Network Protocol Review	Indication. Pre-assessment. Dose modifications. Concurrent medication. Adverse effects. references	June 2018	1.3	June 2020
Myeloma Protocol Review 2019	Update of indication, pre-assessment, dose modification, adverse effects and references	June 2019	1.4	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Update with the new indication during COVID-19 pandemic	June 2020	1.5	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	1.6	June 2021