IXAZOMIB WITH LENALIDOMIDE AND DEXAMETHASONE (IRD)

INDICATION

Relapsed multiple myeloma patients, who have received 2 or 3 prior lines of therapy (i.e. no lines less than 2 and no lines more than 3[a]), in patients that are non-refractory to proteasome inhibitor-based therapy nor to lenalidomide-based treatment (NICE TA870).[b]

[a] The numbering of these lines of treatment is in accordance with the International Myeloma Workshop Consensus recommendations for the uniform reporting of clinical trials (http://doi.org/10.1182/blood-2010-10-299487).

[b] **This indication is not funded for amyloidosis patients** (with the exception of patients with a proven diagnosis of progressive myeloma and who also have an associated diagnosis of amyloidosis).

Blueteq approval 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 / HbA1c, to be monitored regularly
    - 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. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
3. 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.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight, dose on actual body weight.
7. Document patient's performance status
8. Treatment must be agreed at the relevant MDT.
9. Counselling - all patients should receive verbal and written information on oral SACT. Ensure pre-SACT counselling in line with NPSA recommendation and SACT measures.

REGIMEN SPECIFIC PRE-ASSESMENT

1. The conditions of the Lenalidomide Pregnancy Prevention Programme (PPP) must be fulfilled for **all** male and female patients. Prescribing and dispensing of lenalidomide must be in line with programme requirements.
2. Clinical assessment of thrombo-embolic risk.

DRUG REGIMEN

All 3 drugs in the combination must be commenced at the same time in accordance with commissioning criteria i.e., therapy cannot be "added on".

Drug	Starting dose	Days	Administration
Ixazomib*	4 mg once only	1, 8 and 15	Oral 1 hour before, or 2 hours after food
Lenalidomide	25 mg once daily	1 – 21	Oral With or without food
Dexamethasone	40 mg once only **Consider reduction to 20mg once only in the elderly (≥75 years), or if poor steroid tolerance or dexamethasone side effects develop**	1, 8, 15 and 22	Oral In the morning, with food

***If missed or delayed, do not take within 72 hours of next scheduled dose

CYCLE FREQUENCY

Every 28 days 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-haematological toxicities should resolve to at least G1 or baseline.

G-CSF and platelet support can be considered.

Recommended dose reduction levels:

Ixazomib

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

Lenalidomide

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

Recommended dose adjustments due to treatment-related toxicities:

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 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.

Consider re-escalating doses of lenalidomide and/or ixazomib provided toxicities have completely resolved.

Thrombocytopenia	
When platelets	**Recommended Action**
1st occurrence < 30 x 10^9/L	Interrupt treatment*. Reduce **lenalidomide** by one dose level.
Return to ≥ 30 x 10^9/L	Resume treatment.
2nd occurrence < 30 x 10^9/L	Interrupt treatment*. Reduce **ixazomib** by one dose level.
Return to ≥ 30 x 10^9/L	Resume treatment.
3rd or more occurrences < 30 x 10^9/L	Interrupt treatment*. Continue the alternating dose reduction of lenalidomide or ixazomib and resume on FBC recovery.

*Dexamethasone may continue during treatment interruption at the discretion of treating clinician.

Neutropenia

When neutrophils	Recommended Course
1st occurrence < 0.5 x 10^9/L	Interrupt treatment* - give G-CSF for 3 days, check FBC. Reduce **lenalidomide** by one dose level.
Return to ≥ 0.5 x 10^9/L	Resume treatment.
2nd occurrence < 0.5 x 10^9/L	Interrupt treatment* - give G-CSF for 3 days, check FBC. Reduce **ixazomib** by one dose level.
Return to ≥ 0.5 x 10^9/L	Resume treatment.
3rd or more occurrences < 0.5 x 10^9/L	Interrupt treatment* - give G-CSF for 3 days, check FBC. Continue the alternating dose reduction of lenalidomide or ixazomib and resume on FBC recovery.

*Dexamethasone may continue during treatment interruption at the discretion of treating clinician.

Rash

CTCAE 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 ixazomib 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 only)

CTCAE Grading	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. On recovery to ≤ Grade 1 without pain or to patient baseline resume Ixazomib at most recent dose.
Grade 2: As G2 above, with pain. **OR** Grade 3: Severe symptoms; limiting self-care ADL	Withhold ixazomib. On recovery to ≤ Grade 1 or to patient baseline resume Ixazomib at most recent dose.
Grade 4: Life-threatening; urgent intervention indicated, **AND/OR** severe autonomic neuropathy	Discontinue treatment

Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, clinical trials have demonstrated no increase in frequency, or severity grading of peripheral neuropathy when used in combination therapy, or in long term use.

RENAL AND HEPATIC DOSE ADJUSTMENTS:

Lenalidomide		
Renal (CrCl[a])		**Hepatic**
30 - 50 ml/min	10mg once daily*	No formal studies. No specific dose recommendations
< 30 ml/min, no dialysis	15 mg every other day**	
< 30 ml/min, requiring dialysis	5 mg once daily***	

[a] Calculation used to estimate creatinine clearance (CrCl) should follow local institutional standard.

***** Can increase to 15mg OD if no response and patient tolerating.

** Can increase to 10mg OD if no response and patient tolerating.

*** Administer on dialysis day, timing the dose after dialysis as lenalidomide is most likely dialysed.

Ixazomib	
Renal	**Hepatic**
Mild or moderate impairment (CrCl ≥ 30 mL/min) - No dose adjustment Severe impairment or ESRD with dialysis (CrCl < 30 ml/min) - Reduce the starting dose to 3mg. Ixazomib is not dialysable, therefore doses can be administered without timing for dialysis.	Mild impairment (normal bilirubin with AST/ALT > ULN, or bilirubin >1 - 1.5 x ULN) - No dose adjustment. Moderate (bilirubin >1.5 – 3 x ULN)impairment /Severe impairment (bilirubin >3 x ULN) - Reduce starting dose to 3mg.

ALT= Alanine aminotransferase; AST= aspartate aminotransferase; ULN= upper limit of normal; ESRD= end stage renal disease

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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.
- Perform blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance.

CONCURRENT MEDICATION

- Cycle 1 only - Allopurinol 300 mg daily for 7 days (TLS prophylaxis).
- Aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl <10ml/min).
- Fluconazole 50mg OD.
- H2 antagonist

- Apixaban 2.5mg BD (unless other risk factors or drug interactions present, always clinically assess - see thromboprophylaxis information in adverse effects section below
- Bone protection as per NSSG Bone Protection protocol MM.3
    - Note patients will need dental review prior to any bisphosphonate treatment
- Patients deemed high risk of infection **-** Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-3). Adjust dose for renal function. Beware tendonitis risk.
- If heavily pre-treated or prior autograft - consider prophylactic co-trimoxazole 960mg OD on M/W/F

As and when required:

- Onset of diarrhoea: Consider loperamide PRN 4mg stat at first loose stool, then 2mg PRN every 4 hours up to maximum of 16mg in 24 hours.
- Suspicion of bile salt malabsorption with lenalidomide: Consider colestyramine sachets 4 g once daily initially (may need to increase to 2-3 times a day) or colesevelam 2g OD (may need to increase to 2-3 times a day) – unlicensed indication. Colestyramine and Colesevalam may delay or reduce the absorption on other drugs: Lenalidomide, Ixazomib and other medication should be taken 1h before or 6h after Colestyramine. Colesevelam should be taken 4 hours before or 4 hours after Lenalidomide, Ixazomib and other medication.
- Mild nausea/vomiting: Consider metoclopramide 10mg TDS or cyclizine 50mg TDS PRN.

INTERACTIONS

Not exhaustive, for full details consult product literature/ reference texts

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.

Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide.

EMETIC RISK

Minimal emetic risk.

Nausea tends to be associated with Ixazomib administration, consider dose reduction of Ixazomib if uncontrolled nausea/vomiting. Maintaining steroid administration on the days of ixazomib dosing can assist with management.

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 occur between days 14-21 of each 28-day cycle and recover to baseline by the start of the next cycle. Patients should monitor themselves for unusual signs of bleeding or bruising, especially if prophylactic VTE treatments are concomitantly administered. Follow dose modifications for haematological toxicity as per section above.
- **Diarrhoea:** Diarrhoea 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, consider addition of colestyramine.

- **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 not a preference 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 local guidelines.

- **Teratogenic:** The manufacturer's 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 neuropathy of grades 1 and 2 have been reported in up to 25% of patients. Any new or worsening peripheral neuropathy may require dose modification; see above dose modification section.
- **Peripheral oedema:** 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:** Pruritic maculopapular and macular rashes are commonly reported and are usually mild-moderate in severity. Incidence is generally highest in the first 3 months of therapy. Management can follow usual supportive care measures (e.g., topical corticosteroid and/or oral antihistamines) and dose modifications as above. Grade 4 rashes should prompt discontinuation.
- **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, BMS, May 2021
3. NINLARLO® eMC UK Summary of Product Characteristics for, Takeda, Feb 2021

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
NSSG Myeloma Group	Annual myeloma protocol review 2021	June 2021	1.7	June 2022
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	1.8	June 2023
NSSG Myeloma Group	Update of funding from CDF to NHSE and respective NICE TA. Removal of COVID-19 indication. Minor formatting. Addition of dosing info for colestyramine/colesevelam. Addition of Apixaban 2.5mg BD as preferred VTE prophylaxis. Rewording in some sections to condense info.	June 2023	2.0	June 2024