Ixazomib with Lenalidomide and Dexamethasone

INDICATION: Relapsed or refractory multiple myeloma patients, who have received two or more prior lines of therapy. The manufacturer will meet the drug cost of lenalidomide for people remaining on the treatment for more than 26 cycles.

Ixazomib is licensed and NICE approved in England for use through the Cancer Drugs Fund for use in patients who have had 2 or 3 prior lines of therapy. Patients must be registered on blueteq prior to commencing treatment

Prior to a course of treatment

- FBC, Clotting screen,U&Es, LFTs, TSH, Random glucose, Calcium, Albumin, β2 microglobulin, Uric acid
- ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
- Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
- Electrophoresis and immunofixation and Serum free light chain assay
- eGFR
- Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions
- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle**.**
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss (low) risk of infertility - offer semen cryopreservation to male patients
- Written consent
- Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients
- Clinical Assessment of thrombo-embolic risk

Prior to each dose

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC, U&Es, creat, LFTs - neuts must be >1.0 and platelets > 70 – *see dose modifications*

Ixazomib	Starting dose is 4 mg	PO	Once weekly on days 1,8, and 15
Lenalidomide	Starting dose is 25 mg	PO	Once daily on days 1 to 21
Dexamethasone	40 mg Consider 20mg in the elderly or if developed steroid-related side effects	PO	Once weekly on days 1,8,15 & 22

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.

Repeat cycle every 28 days until disease progression or unacceptable toxicity

Prophylaxis for acute emesis Low emetic Risk

Prophylaxis for delayed emesis

Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1 Prophylactic acyclovir 400mg bd recommended Prophylactic fluconazole 50mg OD if appropriate Prophylactic co-trimoxazole if heavily pre-treated or previous autograft. Prophylactic dose LMWH/Aspirin can also be considered Consider a PPI at clinician's discretion Bisphosphonates as per protocol. Loperamide 4mg stat then 2mg prn every 4 hours up to maximum of 16mg in 24 hours to start at the first episode of diarrhea Consider cholestyramine if suspicion of bile salt malabsorption with Lenalidomide Consider metoclopramide or cyclizine when required if nausea and/or vomiting experienced

Dose Modifications

Ixazomib dose reduction levels

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

Lenalidomide dose reduction levels

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

Dose modification for haematological toxicity (unless due to disease)

- 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 lenalidomide and/or ixazomib dose provided toxicities have completely resolved.

Thrombocytopenia:

Platelets	**Recommendation**
First fall to < 30 x 109/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 109/L	Resume **lenalidomide** at its **next lower** dose Resume Ixazomib at its most recent dose.
Second fall to < 30 x 109/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 109/L	Resume lenalidomide at its most recent dose Resume **ixazomib** at the **next lower** dose.
For each subsequent drop below 30 x 109/L	Interrupt lenalidomide and ixazomib treatment
Return to ≥ 30 x 109/L	Alternate dose modification of lenalidomide and ixazomib

Neutropenia:

Neutrophils	**Recommendation**
First fall to < 0.5 x 109/L	Interrupt lenalidomide and ixazomib treatment. Administer G-CSF for 3 days and recheck FBC
Return to ≥ 0.5 x 109/L when neutropenia is the only observed toxicity	Resume **lenalidomide** at its **next lower** dose Resume Ixazomib at its most recent dose.
Second fall to < 0.5 x 109/L	Interrupt lenalidomide and ixazomib treatment Administer G-CSF for 3 days and recheck FBC
Return to ≥ 0.5 x 109/L	Resume lenalidomide at its most recent dose Resume **ixazomib** at the **next lower** dose.
For each subsequent drop below < 0.5 x 109/L	Alternate dose modification of lenalidomide and ixazomib

Rash:

Grade	Recommendation
2 or 3	**1st occurrence:** withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1, Then resume **lenalidomide** at the next lower dose. If tolerated, escalate lenalidomide dose in subsequent cycles. Once patient established, re-introduce ixazomib at the 2nd reduction level. **2nd occurrence:** withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1 then resume **lenalidomide** at the next lower dose and discontinue Ixazomib. **Subsequent occurrence:** Consider alternate dose modification of lenalidomide and ixazomib.
4	**Discontinue treatment regimen**

Peripheral neuropathy:

Grade	Recommendation
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/O**R *severe autonomic neuropathy*	Discontinue treatment

Lenalidomide:

Renal dysfunction	Liver dysfunction
CrCl 30- 50 ml/min 10mg once daily* CrCl < 30 ml/min, no dialysis 15 mg every other day** CrCl < 30 ml/min, requiring dialysis 5 mg once daily***	No specific recommendations

*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 dysfunction	Liver dysfunction
Reduce the starting dose to 3mg if CrCl < 30 ml/min or end-stage renal disease requiring dialysis.	Reduce the starting dose to 3mg in moderate (total bilirubin >1.5-3 x ULN) or severe (total Bilirubin >3 x ULN) impairment.

Toxicities

Myelosuppression
Diarrhoea
Other Gastrointestinal Toxicities: constipation, nausea, and vomiting,
Venous thromboembolism (VTE)
Peripheral Neuropathy
Peripheral Edema
Cutaneous Reactions
Teratogenicity
Hepatotoxicity
Hypothyroidism

Increased risk of secondary malignancies with Lenalidomide -MHRA Alert

Posterior reversible encephalopathy syndrome (PRES)- In patients developing PRES, discontinue ixazomib

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Date	October 2019
Review date	November 2021

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, 23 May 2019
3. NINLARLO® eMC UK Summary of Product Characteristics for, Takeda, 03 October 2018