Ixazomib, Lenalidomide and Dexamethasone Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	C90	00516a	CDS 1/12/2018

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ixazomib is administered once weekly on Days 1, 8, and 15, dexamethasone on Days 1, 8, 15, and 22 and lenalidomide on Day 1- 21 in a 28-day treatment cycle (Table 1).

Treatment should be continued until disease progression or unacceptable toxicity. Treatment for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited.

Table 1: Treatment table for ixazomib

Day	Drug	Dose	Route of administration	Cycle
1, 8 and 15	Ixazomib	4mg	PO[a]	Every 28 days
1-21 inclusive	Lenalidomide	25mg	PO	Every 28 days
1,8, 15 and 22	Dexamethasone	40mg	PO	Every 28 days
[a]Ixazomib should be taken at least 1 hour before or at least 2 hours after food				
Delayed or missed doses: In the event that an ixazomib dose is delayed or missed, the dose should be taken only if the next scheduled dose is ≥ 72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. A double dose should not be taken to make up for a missed dose. If a patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.				

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- ANC > 1 x 10^9/L, platelets > 75 x 10^9/L
- CrCl ≥30ml/min

CAUTIONS:

- Pre-existing neuropathy
    - Peripheral neuropathy -Grade 1 with pain or Grade ≥ 2

EXCLUSIONS:

- Hypersensitivity to ixazomib, lenalidomide or any of the excipients.
- Pregnancy.
- Breastfeeding
- Women of childbearing potential unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Uric acid
- Blood glucose (patients on oral hypoglycaemics)
- ECG
- Assessment of peripheral neuropathy status
- VTE risk assessment
- Pregnancy test in women of child-bearing age or evidence of a hysterectomy. Assessment and registration as per Pregnancy Prevention Program for both male and female patients.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb)
  *(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- Consider FBC, renal, liver and bone profile on day 14 of cycle 1
- FBC, renal and liver profile monthly thereafter
- Blood glucose
- Pregnancy test every 28 days if female of childbearing potential
- Consider monitoring thyroid function tests
- Peripheral neuropathy assessment

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Prior to initiating a new cycle of therapy:
  - Absolute neutrophil count should be ≥ 1.0 x 10^9/L
  - Platelet count should be ≥ 75x10^9/L
  - Non-haematologic toxicities should, at the clinician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1
- The dose reduction steps for ixazomib and lenalidomide are outlined in Table 2 and dose modification guidelines are provided in Tables 3-5

Table 2: Dose Level Reduction steps for Ixazomib and Lenalidomide

	Ixazomib	Lenalidomide
Recommended starting dose	4mg*	25mg
Dose level -1	3mg	15mg
Dose level -2	2.3mg	10mg
Dose level- 3	DISCONTINUE	5mg

*Recommended reduced dose of 3 mg in the presence of moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease (ESRD) requiring dialysis.

- An alternating dose modification approach is recommended for ixazomib and lenalidomide for overlapping toxicities of thrombocytopenia, neutropenia and rash.
- For these toxicities, the first dose modification step is to withhold/reduce lenalidomide.

Haematological

Table 3: Recommended dose modification guidelines for treatment with ixazomib in combination with lenalidomide and dexamethasone

Haematologic toxicity	Recommended action
Platelet count < 30x10^9/L	
1st occurrence	Withhold ixazomib and lenalidomide until platelet count ≥ 30x10^9/L. Following recovery, resume lenalidomide at the next lower dose level and resume ixazomib at its most recent dose.
2nd occurrence	Withhold ixazomib and lenalidomide until platelet count ≥ 30x10^9/L. Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*
Absolute neutrophil count < 0.5 x 10^9 /L	
1st occurrence	Withhold ixazomib and lenalidomide until ANC is ≥ 0.5 x 10^9 cells/L. Consider adding G-CSF as per clinical guidelines. Following recovery, resume lenalidomide at the next lower dose level and resume ixazomib at its most recent dose.
2nd occurrence	Withhold ixazomib and lenalidomide until ANC is ≥ 0.5 x 10^9 cells/L. Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*

Renal and Hepatic Impairment:

Table 4: Recommended dose modification of ixazomib and lenalidomide based on renal and hepatic function

Drug	Renal		Hepatic
Ixazomib	**Creatinine Clearance (ml/min)**	**Dose modification**	No dose adjustment of ixazomib is required for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1-1.5 x ULN and any AST). The reduced dose of 3 mg is recommended in patients with moderate (total bilirubin > 1.5-3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment.
	≥ 30	No dose adjustment required	
	< 30 or end-stage renal disease (ESRD) requiring dialysis.	Reduce dose to 3mg	
	Ixazomib is not dialyzable and, therefore, can be administered without regard to the timing of dialysis		
Lenalidomide	**Creatinine Clearance (ml/min)**	**Dose modification**	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations
	30 to 50	Reduce dose to 10mg once daily*	
	<30 not requiring dialysis	15mg every other day	
	< 30 requiring dialysis	Reduce dose to 5mg once daily. On dialysis days dose should be administered after dialysis.	
	*The dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment		

Management of adverse events

Table 5: Recommended dose modifications based on adverse events

Adverse event	Dose modification
Rash Grade 2 or 3 • **1st occurrence** • **2nd occurrence** Grade 4	 Withhold lenalidomide until rash recovers to ≤ Grade 1. Following recovery, resume lenalidomide at the next lower dose level 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.* Discontinue treatment regimen
Peripheral neuropathy Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy Grade 4 peripheral neuropathy	 Withhold ixazomib until peripheral neuropathy recovers to ≤ Grade 1 without pain or patient's baseline. Following recovery, resume ixazomib at its most recent dose. Withhold ixazomib. Toxicities should, at the clinician's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming ixazomib. Following recovery, resume ixazomib at the next lower dose. Discontinue treatment regimen
Other Grade 3 or 4 non-haematological toxicities	Withhold ixazomib. Toxicities should, at the clinician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming ixazomib. If attributable to ixazomib, resume ixazomib at the next lower dose following recovery.
*For additional occurrences, alternate dose modification of lenalidomide and ixazomib	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Ixazomib: Minimal to low **(Refer to local policy).**
Lenalidomide: Minimal to low **(Refer to local policy).**

PRE-MEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Antiviral prophylaxis should be prescribed in patients being treated with ixazomib as it has been shown to decrease the risk of herpes zoster reactivation in patients treated with proteasome inhibitors **(Refer to local policy)**
- Tumour Lysis Syndrome (TLS) prophylaxis **(Refer to local policy)**
- Thromboprophylaxis **(Refer to local policy**)
- Prophylactic laxatives to prevent lenalidomide-induced constipation **(Refer to local policy).**
- Bisphosphonates should be considered in all patients with myeloma-related bone disease.
- Consider the use of a H_2 antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Ixazomib and lenalidomide are subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

Ixazomib

- **Thrombocytopenia:** Thrombocytopenia has been reported with ixazomib with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Platelet counts should be monitored at least monthly during ixazomib treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide SmPC. Thrombocytopenia can be managed with dose modifications and platelet transfusions as per standard medical guidelines.
- **Gastrointestinal toxicities** Diarrhoea, constipation, nausea and vomiting have been reported with ixazomib, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care). The dose should be adjusted for severe (Grade 3-4) symptoms In case of severe gastrointestinal events, monitoring of serum potassium level is recommended**.**
- **Peripheral neuropathy:** Peripheral neuropathy has been reported with ixazomib. The patient should be monitored for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.
- **Peripheral oedema:** Peripheral oedema has been reported with ixazomib. The patient should be evaluated for underlying causes and provide supportive care, as necessary. The dose of dexamethasone should be adjusted per its prescribing information or ixazomib for Grade 3 or 4 symptoms**.**
- **Cutaneous reactions:** Rash has been reported with ixazomib and should be managed with supportive care or with dose modification if Grade 2 or higher.
- **Thrombotic microangiopathy**: Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP), have been reported in patients who received ixazomib. Some of these events have been fatal. Signs and symptoms of TMA should be monitored for. If the diagnosis is suspected, stop ixazomib and evaluate patients for possible TMA. If the diagnosis of TMA is excluded, ixazomib can be restarted. The safety of reinitiating ixazomib therapy in patients previously experiencing TMA is not known.
- **Hepatotoxicity:** Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have been uncommonly reported with ixazomib. Hepatic enzymes should be monitored regularly and the dose should be adjusted for Grade 3 or 4 symptoms**.**
- **Pregnancy:** Women should avoid becoming pregnant while being treated with ixazomib. If ixazomib is used during pregnancy or if the patient becomes pregnant while taking ixazomib, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential must use highly effective contraception while taking ixazomib and for 90 days after stopping treatment. Women using hormonal contraceptives should additionally use a barrier method of contraception**.**
- **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
- **Concomitant use of strong CYP3A inducers**: Strong inducers may reduce the efficacy of ixazomib, therefore the concomitant use of strong CYP3A inducers during therapy with ixazomib should be avoided. Closely monitor patients for disease control if co-administration with a strong CYP3A inducer cannot be avoided

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology

Lenalidomide

- **Teratogenetic effects:** Lenalidomide is structurally related to thalidomide a powerful human teratogen. It must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met.
- **Skin reactions:** Lenalidomide must be discontinued permanently for exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected.
- **Cardiovascular:** Patients with known risk factors for MI, including prior thrombosis should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia). There is an increased risk of venous and arterial thromboembolism in patients treated with lenalidomide and dexamethasone. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thromboembolic risk in these patients. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.
- **Peripheral Neuropathy:** Lenalidomide is structurally related to thalidomide which is known to induce severe peripheral neuropathy. The neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.
- **Thyroid function:** Cases of hypothyroidism have been reported and baseline and ongoing monitoring of thyroid function is recommended.
- **Tumour lysis syndrome:** Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.
- **Pulmonary hypertension**: Cases of pulmonary hypertension, some fatal, have been reported in patients treated with lenalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during lenalidomide therapy.

DRUG INTERACTIONS:

- Strong CYP3A inducers may reduce the efficacy of ixazomib; therefore the concomitant use of strong CYP3A inducers should be avoided.
- Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution multiple myeloma patients receiving lenalidomide with dexamethasone.
- There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.
- Oral contraceptives: When ixazomib is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using hormonal contraceptives should additionally use a barrier method of contraception.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Lenalidomide

- Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources
- Prescribers are required to read and understand the relevant HCP Information Guide and to adhere to the PPP

REFERENCES:

1. Moreau P et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;374:1621-34.
2. NINLARO®Summary of Product Characteristics Accessed January 2021.Available at https://www.ema.europa.eu/en/documents/product-information/ninlaro-epar-product-information_en.pdf
3. Revlimid®Summary of Product Characteristics Accessed January 2021.Available at https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	23/10/2018		Dr Patrick Hayden
2	17/05/2021	Regimen review Updated emetogenic potential Updated recommendations regarding management of hepatitis B reactivation Updated adverse effects section with regards to thrombotic microangiopathy for Ixazomib and pulmonary hypertension for lenalidomide.	Dr Patrick Hayden
2a	13/02/2024	Updated company support resources/ useful links section in line with NCCP standardisation.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.