Drug Monograph

A - Drug Name

ixazomib

COMMON TRADE NAME(S): Ninlaro™

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B - Mechanism of Action and Pharmacokinetics

Ixazomib reversibly inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome leading to apoptosis of several tumor cell types in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. Ixazomib has also demonstrated anti-angiogenic effects in vitro.

Absorption	Bioavailability	58% (based on population PK analysis)
	Effects with food	Administration with a high-fat meal: ↓ AUC by 28% and C_{max} by 69% Administration with food: delays T_{max} from 1 hour to 4 hours
Distribution	PPB	99% (primarily serum albumin)
	Distribution Sites	Distributes into red blood cells with blood-to-plasma AUC ratio of 10
Metabolism	Active metabolites	ixazomib citrate (prodrug) rapidly hydrolyzes to the active form, ixazomib, under physiological conditions

	Main enzymes involved	Likely hepatic via multiple CYP enzymes and non-CYP proteins. No specific CYP isoform contributed predominantly at clinically relevant concentrations. Possible CYP isoforms involved in metabolism: CYP3A4, 1A2, 2B6, 2C8, 2D6, 2C19, and 2C9.
Elimination	Half-life	9.5 days
	Urine	62% (<3.5% as unchanged drug)
	Feces	22%

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C - Indications and Status

Health Canada Approvals:

In combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Note: Approval was based on the initial results of a randomized, double-blind, placebo-controlled, multicentre Phase III study in patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy; patients who were refractory to lenalidomide or proteasome inhibitors (any line) were excluded from the study. There was a statistically significant improvement in median progression free survival of approximately 6 months compared to the placebo regimen (20.6 months vs 14.7 months).

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects are from a Phase III, randomized, double-blind, placebo-

controlled study comparing ixazomib in combination with lenalidomide and dexamethasone versus placebo in combination with lenalidomide and dexamethasone. Adverse events where incidence was ≥ 10% and occurred at a higher frequency in the ixazomib group, as well as rare but serious events, are listed.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Cutaneous vasculitis (rare)	E D
	Erythema multiforme (rare)	E D
	Rash, pruritus (19%) (rarely severe- Stevens Johnson syndrome, Toxic epidermal necrolysis)	E D
	Severe rash (rare- DRESS syndrome, acute generalised exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome))	E D
Gastrointestinal	Anorexia (13%)	E
	Constipation (34%)	E
	Diarrhea (42%)	E
	Nausea, vomiting (26%) (generally mild)	E
General	Edema - limbs (25%)	E
	Fatigue (28%)	E
Hematological	Myelosuppression ± infection (30%) (may be severe)	E
	Thrombotic thrombocytopenic purpura (rare)	E
Hepatobiliary	Hepatotoxicity (<1%)	E
Infection	Infection (20%)	E
Metabolic / Endocrine	↓ K (11%)	E
	Tumor lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (21%)	E
Nervous System	Dizziness (13%)	E
	Headache (11%)	E
	Myelitis (rare)	E D
	Peripheral neuropathy (28%)	E D
	RPLS / PRES (rare)	E
Ophthalmic	Eye disorders (26%) (blurred vision, dry eye, conjunctivitis)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ixazomib include diarrhea, constipation, myelosuppression ± infection, peripheral neuropathy, eye disorders, fatigue, nausea, vomiting, peripheral edema, musculoskeletal pain, rash and pruritus.

Adverse events of any type and severe adverse events were reported with similar frequency between the ixazomib and placebo regimens.

Thrombocytopenia was transient and reported in 28% of patients (nadir day 14-21). There was no increase in hemorrhagic events or platelet transfusions.

Hepatic effects, including drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic, hepatotoxicity, and liver impairment have been reported.

Herpes zoster infection has been reported; patients who received antiviral prophylaxis had a lower incidence (<1%) compared to those who did not receive prophylaxis (6%). Antiviral prophylaxis should be considered.

The majority of **peripheral neuropathies** (ususally sensory) were Grade 1 and 2 (Grade 3 - 2%).

Maculopapular rash was reported in 19% of patients, usually in the first 3 months (only 3% severe). When required, medical management included antihistamines (e.g. cetirizine), topical glucocorticoids, and dose adjustments.

Serious cutaneous adverse events, including erythema multiforme, acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis and cutaneous vasculitis have been reported, but are rare.

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E - Dosing

Consider the use of antiviral prophylaxis during ixazomib therapy to decrease the risk of herpes zoster reactivation.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be ≥ 1.0 x 10^9/L
- Platelet count should be ≥75 x 10^9/L
- Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1

Adults:

Ixazomib in combination with lenalidomide and dexamethasone:

Recommended starting doses:

Ixazomib 4mg PO once a week on Days 1, 8, and 15

Lenalidomide 25mg PO once Daily on Days 1 to 21

Dexamethasone 40 mg PO once a week on Days 1, 8, 15, and 22

REPEAT Q 28 DAYS until disease progression or unacceptable toxicity.

28-Day Cycle								
	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Ixazomib	X		X		X			
Lenalidomide	X	daily	X	daily	X	daily		
Dexamethasone	X		X		X		X	

Dosage with Toxicity:

For additional information regarding lenalidomide and dexamethasone, refer to their respective drug monographs.

Table 1: Ixazomib Dose Levels

Dose Level	Ixazomib Dose
Starting Dose*	4 mg
-1	3 mg
-2	2.3 mg
-3	discontinue

* Recommended starting dose of 3 mg in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease requiring dialysis.

Table 2: Dose Modification for Toxicities

An alternating dose modification approach is recommended for ixazomib and lenalidomide for overlapping toxicities (thrombocytopenia, neutropenia, rash). Refer to the lenalidomide drug monograph for dose levels.

Toxicity		**Action**	**Ixazomib Dose when restart**	**Lenalidomide dose when restart**
First Occurrence Platelet count < 30 x 10^9/L OR ANC < 0.5 x 10^9/L		Hold until platelets ≥ 30 AND ANC ≥ 0.5; consider adding G-CSF	No change	1 dose level ↓
Second Occurrence Platelet count < 30 x 10^9/L OR ANC < 0.5 x 10^9/L		Hold until platelets ≥ 30 AND ANC ≥ 0.5; consider adding G-CSF	1 dose level ↓*	No change*
Rash	Grade 2 or 3	Hold both until ≤ Grade 1	Continue at same dose. If recurs, hold until recovery and then resume with 1 dose level ↓	Resume with 1 dose level ↓ Discontinue if ≥ Grade 2 exfoliative skin toxicity or SJS/TEN
	Grade 4	Discontinue	Discontinue	Discontinue

Peripheral Neuropathy	Grade 1 with Pain or Grade 2	Hold ixazomib until ≤ Grade 1 without pain or patient's baseline	Resume at same dose	Continue at same dose
	Grade 2 with pain or Grade 3	Hold both until ≤ Grade 1 without pain or patient's baseline	1 dose level ↓	Consider 1 dose level ↓ if grade 3
	Grade 4	Discontinue	Discontinue	Discontinue
≥ Grade 2 VTE		Hold lenalidomide and start anticoagulants	No change	Resume when recovered at same dose
Other Grade 3 or 4 Non-Hematological Toxicities		Hold both until recovery to baseline or ≤ Grade 1	If toxicity due to ixazomib, resume at 1 dose level ↓ once recovered or discontinue	If toxicity due to lenalidomide, resume at 1 dose level ↓ once recovered or discontinue. If pneumonitis investigate and discontinue if confirmed
Increased LFTS			See table below for dosage with hepatic dysfunction	Hold until recovery then consider dose reduction

*For additional occurrences, alternate dose modification of lenalidomide and ixazomib

Dosage with Hepatic Impairment:

Hepatic impairment	**Ixazomib dose**
mild (total bilirubin ≤ ULN and AST > ULN OR total	no dosage

bilirubin 1-1.5 x ULN and any AST)	adjustment required
moderate or severe (total bilirubin > 1.5 x ULN)	3 mg

Refer to the lenalidomide and dexamethasone drug monographs for recommendations.

Dosage with Renal Impairment:

Renal impairment	**Ixazomib dose**
mild to moderate (CrCl ≥ 30mL/min)	no dosage adjustment required
Severe (CrCl < 30mL/min) or end stage renal disease (ESRD) requiring dialysis*	3 mg

*Ixazomib is not dialyzable and can be administered without regard to the timing of dialysis.

Dosage in the elderly:

No dosage adjustment of ixazomib is required for patients over 65 years of age. No clinically significant differences in safety and efficacy have been demonstrated.

Dosage based on ethnicity:

No clinically significant effect demonstrated during PK analysis; mean AUC was 35% higher in Asian patients than White patients.

Children:

Safety and efficacy in children below 18 years of age has not been established.

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F - Administration Guidelines

- Ixazomib should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a four week cycle.
- The capsule should be swallowed whole with water, on an empty stomach (at least one hour before or at least two hours after food).
- The capsule should not be crushed, chewed, or opened. Direct contact with capsule contents should be avoided as inhalation, ingestion, or skin absorption may be harmful.
- If a dose is missed, it should be taken only if the next scheduled dose is ≥ 72 hours away. 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; resume dosing at the time of the next scheduled dose.
- Store capsules at room temperature (15-30^{o}C) in original packaging. Do not freeze.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- Avoid direct contact with capsule contents; ixazomib may be harmful by inhalation, ingestion, or skin absorption.

Other Drug Properties:

- Carcinogenicity: No information available

Pregnancy and Lactation:

- Fertility effects: Unknown
  Fertility studies were not conducted. There were no effects in reproductive organs in either males or females in nonclinical studies in rats and dogs.
- Fetotoxicity: Probable
  Embryo-fetal toxicity in pregnant rats and rabbits has been documented.
  Ixazomib is not recommended for use in pregnancy. Male and female patients of childbearing potential must use adequate contraception (at least 2 effective measures; at least one must be

a barrier) during treatment, and for at least 3 months after the last dose.
- Breastfeeding: Not recommended
  It is not known whether ixazomib and metabolites are excreted in human milk.

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H - Interactions

The potential for clinically relevant CYP isozyme drug-drug interactions is low. At clinically relevant concentrations, in vitro studies indicate that no specific CYP isoenzyme predominantly contributes to ixazomib metabolism, and non-CYP proteins contribute to overall metabolism. At higher concentrations, ixazomib was metabolized in vitro by multiple CYP isoforms. Ixazomib is not an inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Co-administration with strong CYP3A4 and CYP1A2 inhibitors did not result in clinically significant changes. Co-administration with strong CYP3A4 inducers is not recommended. Ixazomib is unlikely to cause or be susceptible to drug-drug interactions with substrates or inhibitors of transporters. It is a low affinity substrate of P-gp and is not a substrate of BCRP, MPR2, or hepatic OATPs. It is not an inhibitor of OATP1B1, OATP1B3, OCT2, OAT1, MATE1 or MATE2-K.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ ixazomib Cmax by 54% and AUC by 74%	↑ metabolism of ixazomib	Avoid
High-fat meal	↓ ixazomib AUC by 28% and Cmax by 69%	↓ ixazomib absorption	Take on an empty stomach

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

<u>Recommended</u> Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and every 2 weeks for the first 12 weeks, then before each cycle
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Clinical toxicity assessment for infection, bleeding, rash, neuropathy, GI effects, edema, pain, and eye problems.	Baseline and at each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Ninlaro (ixazomib) product monograph. Takeda Canada Inc. August 3, 2016.

Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 374:1621-1634.

June 2019 Updated emetic risk category.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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