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## Ninlaro® 2.3 mg, 3 mg and 4 mg

### Capsules

### Contains Ixazomib (As Citrate) 2.3 mg, 3 mg and 4 mg

#### FULL PRESCRIBING INFORMATION

##### 1 INDICATIONS AND USAGE

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

##### 2 DOSAGE AND ADMINISTRATION

###### 2.1 Dosing and Administration Guidelines

*NINLARO in combination with lenalidomide and dexamethasone*

The recommended starting dose of NINLARO is 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle.

The recommended starting dose of lenalidomide is 25 mg administered daily on Days 1 through 21 of a 28-day treatment cycle.

The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

**Table 1: Dosing Schedule for NINLARO taken with Lenalidomide and Dexamethasone**

✓ Take medicine

28-Day Cycle (a 4-week 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
NINLARO	✓		✓		✓			
Lenalidomide	✓	✓ Daily	✓	✓ Daily	✓	✓ Daily		
Dexamethasone	✓		✓		✓		✓	

For additional information regarding lenalidomide and dexamethasone, refer to their prescribing information.

NINLARO should be taken once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. NINLARO should be taken at least one hour before or at least two hours after food [see *Clinical Pharmacology (11.3)*]. The whole capsule should be swallowed with water. The capsule should not be crushed, chewed or opened [see *How Supplied/Storage and Handling (15.3)*].

If a NINLARO dose is delayed or missed, the dose should be taken only if the next scheduled dose is  $\geq 72$  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 the missed dose.

If vomiting occurs after taking a dose, the patient should not repeat the dose. The patient should resume dosing at the time of the next scheduled dose.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be at least  $1,000/\text{mm}^3$
- Platelet count should be at least  $75,000/\text{mm}^3$
- Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or Grade 1 or lower

Treatment should be continued until disease progression or unacceptable toxicity.

**Concomitant Medications** Consider antiviral prophylaxis in patients being treated with NINLARO to decrease the risk of herpes

zoster reactivation [see *Adverse Reactions* (6.1)].

## 2.2 Dose Modification Guidelines

The NINLARO dose reduction steps are presented in Table 2 and the dose modification guidelines are provided in Table 3.

**Table 2: NINLARO Dose Reductions due to Adverse Reactions**

Recommended starting dose*	First reduction to	Second reduction to	Discontinue
4 mg	3 mg	2.3 mg	

\*Recommended starting dose of 3 mg in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease requiring dialysis [see *Dosage and Administration* (2.3, 2.4)].

An alternating dose modification approach is recommended for NINLARO and lenalidomide for thrombocytopenia, neutropenia, and rash as described in Table 3. Refer to the lenalidomide prescribing information if dose reduction is needed for lenalidomide.

**Table 3: Dose Modifications Guidelines for NINLARO in Combination with Lenalidomide and Dexamethasone**

Hematological Toxicities	Recommended Actions
<b>Thrombocytopenia (Platelet Count)</b>	
Platelet count less than $30,000/\text{mm}^3$	<ul style="list-style-type: none"> <li>• Withhold NINLARO and lenalidomide until platelet count is at least <math>30,000/\text{mm}^3</math>.</li> <li>• Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume NINLARO at its most recent dose.</li> <li>• If platelet count falls to less than <math>30,000/\text{mm}^3</math> again, withhold NINLARO and lenalidomide until platelet count is at least <math>30,000/\text{mm}^3</math>.</li> <li>• Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*</li> </ul>

**Table 3: Dose Modifications Guidelines for NINLARO in Combination with Lenalidomide and Dexamethasone**

<b>Neutropenia (Absolute Neutrophil Count)</b>	
Absolute neutrophil count less than 500/mm <sup>3</sup>	<ul style="list-style-type: none"> <li>• Withhold NINLARO and lenalidomide until absolute neutrophil count is at least 500/mm<sup>3</sup>. Consider adding G-CSF as per clinical guidelines.</li> <li>• Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume NINLARO at its most recent dose.</li> <li>• If absolute neutrophil count falls to less than 500/mm<sup>3</sup> again, withhold NINLARO and lenalidomide until absolute neutrophil count is at least 500/mm<sup>3</sup>.</li> <li>• Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*</li> </ul>
<b>Non-Hematological Toxicities</b>	<b>Recommended Actions</b>
<b>Rash</b>	
Grade <sup>†</sup> 2 or 3	<ul style="list-style-type: none"> <li>• Withhold lenalidomide until rash recovers to Grade 1 or lower.</li> <li>• Following recovery, resume lenalidomide at the next lower dose according to its prescribing information.</li> <li>• If Grade 2 or 3 rash occurs again, withhold NINLARO and lenalidomide until rash recovers to Grade 1 or lower.</li> <li>• Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*</li> </ul>
Grade 4	Discontinue treatment regimen.
<b>Peripheral Neuropathy</b>	
Grade 1 Peripheral Neuropathy with Pain or Grade 2 Peripheral Neuropathy	<ul style="list-style-type: none"> <li>• Withhold NINLARO until peripheral neuropathy recovers to Grade 1 or lower without pain or patient's baseline.</li> <li>• Following recovery, resume NINLARO at its most recent dose.</li> </ul>
Grade 2 Peripheral Neuropathy with Pain or Grade 3 Peripheral Neuropathy	<ul style="list-style-type: none"> <li>• Withhold NINLARO. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming NINLARO.</li> <li>• Following recovery, resume NINLARO at the next lower dose.</li> </ul>
Grade 4 Peripheral Neuropathy	Discontinue treatment regimen.
<b>Other Non-Hematological Toxicities</b>	
Other Grade 3 or 4 Non-Hematological Toxicities	<ul style="list-style-type: none"> <li>• Withhold NINLARO. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming NINLARO.</li> <li>• If attributable to NINLARO, resume NINLARO at the next lower dose following recovery.</li> </ul>

\*For additional occurrences, alternate dose modification of lenalidomide and NINLARO

<sup>†</sup>Grading based on National Cancer Institute Common Terminology Criteria (CTCAE) Version 4.03

## 2.3 Dosage in Patients with Hepatic Impairment

Reduce the starting dose of NINLARO to 3 mg in patients with moderate (total bilirubin greater than 1.5-3 x ULN) or severe (total bilirubin greater than 3 x ULN) hepatic impairment [see *Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)*].

## 2.4 Dosage in Patients with Renal Impairment

Reduce the starting dose of NINLARO to 3 mg in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease (ESRD) requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis [see *Use in Specific Populations (8.7) and Clinical Pharmacology (11.3)*].

Refer to the lenalidomide prescribing information for dosing recommendations in patients with renal impairment.

## 3 DOSAGE FORMS AND STRENGTHS

NINLARO is available in the following capsule strengths:

- 4 mg: Light orange gelatin capsule imprinted with “Takeda” on the cap and “4 mg” on the body in black ink. NINLARO 4 mg capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.
- 3 mg: Light grey gelatin capsule imprinted with “Takeda” on the cap and “3 mg” on the body in black ink. NINLARO 3 mg capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.
- 2.3 mg: Light pink gelatin capsule imprinted with “Takeda” on the cap and “2.3 mg” on the body in black ink. NINLARO 2.3 mg capsules contain 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.

## 4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 14.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombocytopenia

Thrombocytopenia has been reported with NINLARO 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. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count  $\leq 10,000/\text{mm}^3$  during treatment. Less than 1% of patients in both regimens had a platelet count  $\leq 5000/\text{mm}^3$  during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs). The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications [see *Dosage and Administration (2.2)*] and platelet transfusions as per standard medical guidelines.

## 5.2 Gastrointestinal Toxicities

Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms [*see Dosage and Administration (2.2)*].

## 5.3 Peripheral Neuropathy

The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions.

The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification [*see Dosage and Administration (2.2)*].

## 5.4 Peripheral Edema

Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms [*see Dosage and Administration (2.2)*].

## 5.5 Cutaneous Reactions

Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash.

Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher [*see Dosage and Administration (2.2)*].

## 5.6 Thrombotic Microangiopathy

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

## 5.7 Hepatotoxicity

Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen).

Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms [*see Dosage and Administration (2.2)*].

## 5.8 Embryo-Fetal Toxicity

NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using NINLARO. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with NINLARO and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception [*see Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (12.1)*].

# 6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Thrombocytopenia [*see Warnings and Precautions (5.1)*]
- Gastrointestinal Toxicities [*see Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [*see Warnings and Precautions (5.3)*]
- Peripheral Edema [*see Warnings and Precautions (5.4)*]
- Cutaneous Reactions [*see Warnings and Precautions (5.5)*]
- Thrombotic Microangiopathy [*see Warnings and Precautions (5.6)*]
- Hepatotoxicity [*see Warnings and Precautions (5.7)*]

## 6.1 Clinical Trials Experience

The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reactions ( $\geq 20\%$ ) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in  $\geq 2\%$  of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in  $\leq 1\%$  of patients in the NINLARO regimen.

Table 4 summarizes the adverse reactions occurring in at least 5% of patients with at least a 5% difference between the NINLARO regimen and the placebo regimen.

**Table 4: Non-Hematologic Adverse Reactions Occurring in  $\geq 5\%$  of Patients with a  $\geq 5\%$  Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)**

	<b>NINLARO + Lenalidomide and Dexamethasone N=360</b>			<b>Placebo + Lenalidomide and Dexamethasone N=360</b>		
<b>System Organ Class / Preferred Term</b>	<b>N (%)</b>			<b>N (%)</b>		
	<b>All</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>All</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Infections and infestations</b>						
Upper respiratory tract infection	69 (19)	1 (< 1)	0	52 (14)	2 (< 1)	0
<b>Nervous system disorders</b>						
Peripheral neuropathies*	100 (28)	7 (2)	0	77 (21)	7 (2)	0
<b>Gastrointestinal disorders</b>						
Diarrhea	151 (42)	22 (6)	0	130 (36)	8 (2)	0
Constipation	122 (34)	1 (< 1)	0	90 (25)	1 (< 1)	0
Nausea	92 (26)	6 (2)	0	74 (21)	0	0
Vomiting	79 (22)	4 (1)	0	38 (11)	2 (< 1)	0
<b>Skin and subcutaneous tissue disorders</b>						
Rash*	68 (19)	9 (3)	0	38 (11)	5 (1)	0
<b>Musculoskeletal and connective tissue disorders</b>						
Back pain	74 (21)	2 (< 1)	0	57 (16)	9 (3)	0
<b>General disorders and administration site conditions</b>						
Edema peripheral	91 (25)	8 (2)	0	66 (18)	4 (1)	0

**Note:** Adverse reactions included as preferred terms are based on MedDRA version 16.0.

\*Represents a pooling of preferred terms

Table 5 represents pooled information from adverse event and laboratory data.

**Table 5: Thrombocytopenia and Neutropenia**

	<b>NINLARO + Lenalidomide and Dexamethasone N=360</b>		<b>Placebo + Lenalidomide and Dexamethasone N=360</b>	
	<b>N (%)</b>		<b>N (%)</b>	
	<b>Any Grade</b>	<b>Grade 3-4</b>	<b>Any Grade</b>	<b>Grade 3-4</b>
Thrombocytopenia	281 (78)	93 (26)	196 (54)	39 (11)
Neutropenia	240 (67)	93 (26)	239 (66)	107 (30)

### Herpes Zoster

Herpes zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the physician's discretion. Patients treated in the NINLARO regimen who received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

### Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

### Adverse Reactions Reported Outside of the Randomized Controlled Trial

The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

## **7 DRUG INTERACTIONS**

### **7.1 Strong CYP3A Inducers**

Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort) [see *Clinical Pharmacology* (11.3)].



## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Risk Summary*

Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (11.1)*]. There are no human data available regarding the potential effect of NINLARO on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose (see *Data*). Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### *Data*

#### Animal Data

In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (fused caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic ( $\geq 0.3$  mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.6mg/kg. Exposures in rats at the dose of 0.6mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

### **8.2 Lactation**

#### *Risk Summary*

No data are available regarding the presence of NINLARO or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because the potential for serious adverse reactions from NINLARO in breastfed infants is unknown, advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

### **8.3 Females and Males of Reproductive Potential**

#### *Contraception*

Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Advise women using hormonal contraceptives to also use a barrier method of contraception.

### **8.4 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

### **8.5 Geriatric Use**

Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly

and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## 8.6 Hepatic Impairment

In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (11.3)].

## 8.7 Renal Impairment

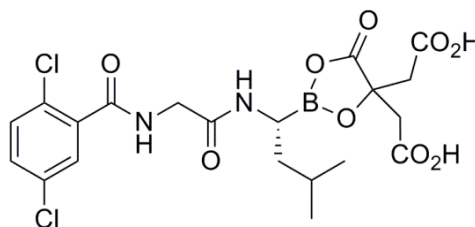
In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis [see *Dosage and Administration* (2.4), *Clinical Pharmacology* (11.3)].

## 9 OVERDOSAGE

There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient for adverse reactions [see *Adverse Reactions* (6.1)] and provide appropriate supportive care.

## 10 DESCRIPTION

Ixazomib is a proteasome inhibitor. Ixazomib citrate, a prodrug, rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib. The chemical name of ixazomib citrate is 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1R)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo- and the structural formula is:



The molecular formula for ixazomib citrate is  $C_{20}H_{23}BCl_2N_2O_9$  and its molecular weight is 517.12. Ixazomib citrate has one chiral center and is the R-stereoisomer. The solubility of ixazomib citrate in 0.1N HCl (pH 1.2) at 37°C is 0.61 mg/mL (reported as ixazomib). The solubility increases as the pH increases.

NINLARO (ixazomib) capsules for oral use contain 4, 3 or 2.3 mg of ixazomib equivalent to 5.7, 4.3 or 3.3 mg of ixazomib citrate, respectively. Inactive ingredients include microcrystalline cellulose, magnesium stearate, and talc. Capsule shells contain gelatin and titanium dioxide. The 4 mg capsule shell contains red and yellow iron oxide, the 3 mg capsule shell contains black iron oxide and the 2.3 mg capsule shell contains red iron oxide. The printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

## 11 CLINICAL PHARMACOLOGY

### 11.1 Mechanism of Action

Ixazomib is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib induced apoptosis of multiple myeloma cell lines in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in a mouse

multiple myeloma tumor xenograft model.

## **11.2 Pharmacodynamics**

### *Cardiac Electrophysiology*

NINLARO did not prolong the QTc interval at clinically relevant exposures based on pharmacokinetic-pharmacodynamic analysis of data from 245 patients.

## **11.3 Pharmacokinetics**

### *Absorption*

After oral administration, the median time to achieve peak ixazomib plasma concentrations was one hour. The mean absolute oral bioavailability was 58%, based on population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 to 10.6 mg.

A food effect study conducted in patients with a single 4 mg dose of ixazomib showed that a high-fat meal decreased ixazomib AUC by 28% and  $C_{\max}$  by 69% [see *Dosage and Administration (2.1)*].

### *Distribution*

Ixazomib is 99% bound to plasma proteins and distributes into red blood cells with a blood-to-plasma ratio of 10. The steady-state volume of distribution is 543 L.

### *Elimination*

Based on a population PK analysis, systemic clearance was approximately 1.9 L/hr with inter-individual variability of 44%. The terminal half-life ( $t_{1/2}$ ) of ixazomib was 9.5 days. Following weekly oral dosing, the accumulation ratio was determined to be 2-fold.

### Metabolism

After oral administration of a radiolabeled dose, ixazomib represented 70% of total drug-related material in plasma. Metabolism by multiple CYP enzymes and non-CYP proteins is expected to be the major clearance mechanism for ixazomib. At clinically relevant ixazomib concentrations, in vitro studies using human cDNA-expressed cytochrome P450 isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib metabolism. At higher than clinical concentrations, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (< 1%).

### Excretion

After administration of a single oral dose of  $^{14}\text{C}$ -ixazomib to 5 patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in the feces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

### *Specific Populations*

There was no clinically meaningful effect of age (range 23-91 years), sex, body surface area (range 1.2-2.7  $\text{m}^2$ ), or race on the clearance of ixazomib based on population PK analysis.

### *Patients with Hepatic Impairment*

The PK of ixazomib was similar in patients with normal hepatic function and in patients with mild hepatic impairment (total bilirubin  $\leq$  ULN and AST  $>$  ULN or total bilirubin  $>$  1-1.5 x ULN and any AST) based on population PK analysis.

The PK of ixazomib was characterized in patients with normal hepatic function at 4 mg (N=12), moderate

hepatic impairment at 2.3 mg (total bilirubin > 1.5-3 x ULN, N=13) or severe hepatic impairment at 1.5 mg (total bilirubin > 3 x ULN, N=18). Dose-normalized mean AUC was 20% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function [*see Dosage and Administration (2.3)*].

#### *Patients with Renal Impairment*

The PK of ixazomib was similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance  $\geq 30$  mL/min) based on population PK analysis.

The PK of ixazomib was characterized at a dose of 3 mg in patients with normal renal function (creatinine clearance  $\geq 90$  mL/min, N=18), severe renal impairment (creatinine clearance < 30 mL/min, N=14), or ESRD requiring dialysis (N=6). Mean AUC was 39% higher in patients with severe renal impairment or ESRD requiring dialysis as compared to patients with normal renal function. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not dialyzable [*see Dosage and Administration (2.4)*].

#### Drug Interaction Studies

##### *Effect of Other Drugs on NINLARO*

###### *Strong CYP3A Inducers*

Co-administration of NINLARO with rifampin decreased ixazomib  $C_{\max}$  by 54% and AUC by 74% [*see Drug Interactions (7.1)*].

###### *Strong CYP3A Inhibitors*

Co-administration of NINLARO with clarithromycin did not result in a clinically meaningful change in the systemic exposure of ixazomib.

###### *Strong CYP1A2 Inhibitors*

Co-administration of NINLARO with strong CYP1A2 inhibitors did not result in a clinically meaningful change in the systemic exposure of ixazomib based on a population PK analysis.

##### *Effect of NINLARO on Other Drugs*

Ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immunoreactive protein levels. NINLARO is not expected to produce drug-drug interactions via CYP inhibition or induction.

##### *Transporter-Based Interactions*

Ixazomib is a low affinity substrate of P-gp. Ixazomib is not a substrate of BCRP, MRP2 or hepatic OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. NINLARO is not expected to cause transporter-mediated drug-drug interactions.

## **12 NONCLINICAL TOXICOLOGY**

### **12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay). Ixazomib was considered positive in an in vitro clastogenicity test in human peripheral blood lymphocytes.

However, in vivo, ixazomib was not clastogenic in a bone marrow micronucleus assay in mice and was negative in an in vivo comet assay in mice, as assessed in the stomach and liver. No carcinogenicity studies have been performed with ixazomib.

Developmental toxicity studies in rats and rabbits did not show direct embryo-fetal toxicity below maternally

toxic doses of ixazomib. Studies of fertility and early embryonic development and pre- and postnatal toxicology were not conducted with ixazomib, but evaluation of reproductive tissues was conducted in the general toxicity studies. There were no effects due to ixazomib treatment on male or female reproductive organs in studies up to 6-months duration in rats and up to 9-months duration in dogs.

### 13 CLINICAL STUDIES

The efficacy and safety of NINLARO in combination with lenalidomide and dexamethasone was evaluated in a randomized, double-blind, placebo-controlled, multicenter 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 were excluded from the study.

A total of 722 patients were randomized in a 1:1 ratio to receive either the combination of NINLARO, lenalidomide and dexamethasone (N=360; NINLARO regimen) or the combination of placebo, lenalidomide and dexamethasone (N=362; placebo regimen) until disease progression or unacceptable toxicity. Randomization was stratified according to number of prior lines of therapy (1 versus 2 or 3), myeloma International Staging System (ISS) (stage I or II versus III), and previous therapy with a proteasome inhibitor (exposed or naïve). Twenty three percent (N=166) of the patients had light chain disease and 12% (N=87) of patients had free light chain-measurable only disease.

Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide prescribing information. Antiemetics were used in 19% of patients in the NINLARO regimen and 12% of patients in the placebo regimen; antivirals in 64% and 60%, respectively, and antihistamines in 27% and 19%, respectively. These medications were given to patients at the physician's discretion as prophylaxis and/or management of symptoms.

Patients received NINLARO 4 mg or placebo on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients with renal impairment received a starting dose of lenalidomide according to its prescribing information. Treatment continued until disease progression or unacceptable toxicities.

Table 6 summarizes the baseline patient and disease characteristics in the study. The baseline demographics and disease characteristics were balanced and comparable between the study regimens.

**Table 6: Baseline Patient and Disease Characteristics**

	<b>NINLARO + Lenalidomide and Dexamethasone (N = 360)</b>	<b>Placebo + Lenalidomide and Dexamethasone (N = 362)</b>
<i>Patient Characteristics</i>		
Median age in years (range)	66 (38, 91)	66 (30, 89)
Gender (%) Male/ Female	58/42	56/44
Age Group (% [< 65/ ≥ 65 years])	41/59	43/57
Race n (%)		
White	310 (86)	301 (83)
Black	7 (2)	6 (2)
Asian	30 (8)	34 (9)
Other or Not Specified	13 (4)	21 (6)
ECOG performance status, n (%)		
0 or 1	336 (93)	334 (92)
2	18 (5)	24 (7)
Missing	6 (2)	4 (1)

Creatinine clearance, n (%)		
< 30 mL/min	5 (1)	5 (1)
30-59 mL/min	74 (21)	95 (26)
≥ 60 mL/min	281 (78)	261 (72)
<i>Disease Characteristics</i>		
Myeloma ISS stage, n (%)		
Stage I or II	315 (87)	320 (88)
Stage III	45 (13)	42 (12)
Prior line therapies n (%)		
Median (range)	1 (1, 3)	1 (1,3)
1	224 (62)	217 (60)
2 or 3	136 (38)	145 (40)
Status at Baseline n (%)		
Relapsed	276 (77)	280 (77)
Refractory*	42 (12)	40 (11)
Relapsed and Refractory	41 (11)	42 (12)
Type of Prior Therapy n (%)		
Bortezomib containing	248 (69)	250 (69)
Carfilzomib containing	1 (<1)	4 (1)
Thalidomide containing	157 (44)	170 (47)
Lenalidomide containing	44 (12)	44 (12)
Melphalan containing	293 (81)	291 (80)
Stem cell transplantation	212 (59)	199 (55)
High risk (deletion (del) 17, t(4:14) and/or t(14:16)	75 (21)	62 (17)
deletion del (17)	36 (10)	33 (9)

\*Primary refractory, defined as best response of stable disease or disease progression on all prior lines of therapy was documented in 7% and 6% of patients in the NINLARO regimen and placebo regimens, respectively.

The efficacy of NINLARO was evaluated by progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central lab results. Response was assessed every four weeks until disease progression.

The approval of NINLARO was based upon a statistically significant improvement in PFS of the NINLARO regimen compared to the placebo regimen. PFS results are summarized in Table 7 and shown in Figure 1.

**Table 7: Progression-Free Survival and Response Rate**

	NINLARO + Lenalidomide and Dexamethasone (N = 360)	Placebo + Lenalidomide and Dexamethasone (N = 362)
Progression-free Survival		
PFS Events, n (%)	129 (36)	157 (43)
Median (months) (95% CI)	20.6 (17.0, NE)	14.7 (12.9, 17.6)
Hazard Ratio* (95% CI)	0.74 (0.59, 0.94)	
p-value†	0.012	
Response Rate		
Overall Response Rate, n (%)	282 (78)	259 (72)
Complete Response	42 (12)	24 (7)
Very Good Partial Response	131 (36)	117 (32)
Partial Response	109 (30)	118 (33)

NE: Not evaluable.

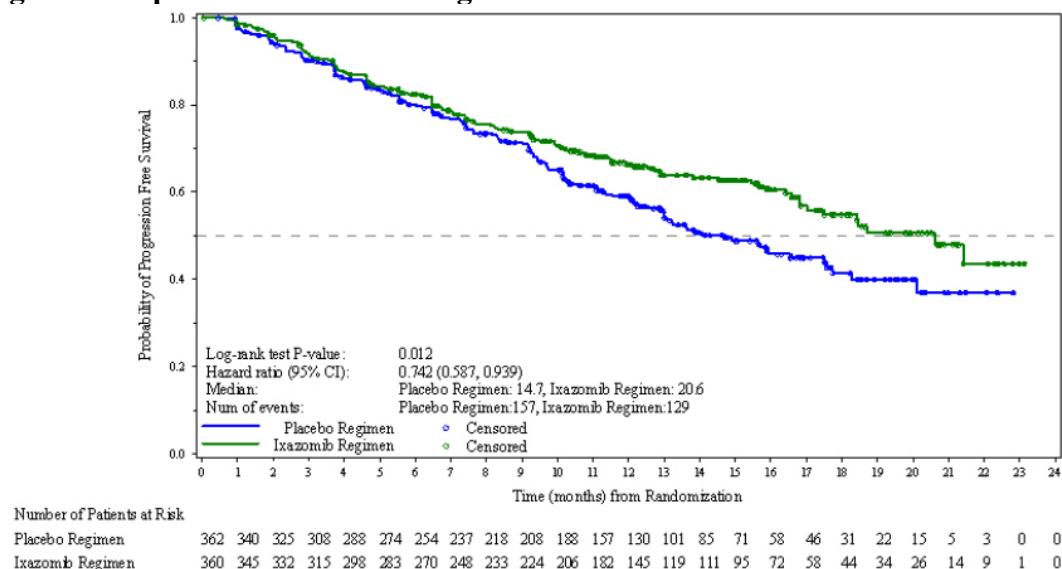
\*Hazard ratio is based on a stratified Cox's proportional hazard regression model. A hazard ratio less than 1 indicates an advantage

for the NINLARO regimen.

<sup>†</sup>P-value is based on the stratified log-rank test.

The median time to response was 1.1 months in the NINLARO regimen and 1.9 months in the placebo regimen. The median duration of response was 20.5 months in the NINLARO regimen and 15 months in the placebo regimen for responders in the response evaluable population.

**Figure 1: Kaplan-Meier Plot of Progression-Free Survival**



A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. Hazard ratio of PFS was 0.82 (95% confidence interval [0.67, 1.0]) for NINLARO regimen versus placebo regimen, and estimated median PFS was 20 months in the NINLARO regimen and 15.9 months in the placebo regimen. At the same time, a planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the NINLARO regimen and 90 deaths in the placebo regimen. An OS benefit was not demonstrated.

## 14 LIST OF EXCIPENTS

### NINLARO 2.3 mg hard capsules

#### Capsule contents

Microcrystalline cellulose

Talc

Magnesium stearate

#### Capsule shell

Gelatin

Titanium dioxide

Red iron oxide

#### Printing ink

Shellac

Propylene glycol

Potassium hydroxide

Black iron oxide

### NINLARO 3 mg hard capsules

#### Capsule contents

Microcrystalline cellulose

Talc

Magnesium stearate

#### Capsule shell

Gelatin  
Titanium dioxide  
Black iron oxide  
Printing ink  
Shellac  
Propylene glycol  
Potassium hydroxide  
Black iron oxide  
NINLARO 4 mg hard capsules  
Capsule contents  
Microcrystalline cellulose  
Talc  
Magnesium stearate  
Capsule shell  
Gelatin  
Titanium dioxide  
Yellow iron oxide  
Red iron oxide  
Printing ink  
Shellac  
Propylene glycol  
Potassium hydroxide  
Black iron oxide

## **15 HOW SUPPLIED/STORAGE AND HANDLING**

### **15.1 How Supplied**

NINLARO is supplied as:

4 mg gelatin capsule: Light orange, size 3, imprinted with “Takeda” on the cap and “4 mg” on the body in black ink. NINLARO 4 mg capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.

- One 4 mg capsule in a single blister pack
- Three 4 mg single packs in a carton

3 mg gelatin capsule: Light grey, size 4, imprinted with “Takeda” on the cap and “3 mg” on the body in black ink. NINLARO 3 mg capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.

- One 3 mg capsule in a single blister pack
- Three 3 mg single packs in a carton

2.3 mg gelatin capsule: Light pink, size 4, imprinted with “Takeda” on the cap and “2.3 mg” on the body in black ink. NINLARO 2.3 mg capsules contain 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.

- One 2.3 mg capsule in a single blister pack
- Three 2.3 mg single packs in a carton

Capsules are individually packaged in a PVC-Aluminum/Aluminum blister.

### **15.2 Storage**

Do not store above 30°C. Do not freeze. Store capsules in original packaging until immediately prior to use.



The expiry date of the product is indicated on the packaging materials.

### **15.3 Handling and Disposal**

NINLARO is a cytotoxic drug. Do not open or crush capsules. Avoid direct contact with the capsule contents. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

#### **Manufactured by:**

Takeda Pharma A/S, Dybendal Alle 10, Taastrup, 2630 Denmark

#### **Registration Holder:**

Takeda Israel Ltd., 25 Eyal St., Petach Tikva 4951125

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156-81-34609-00/01

156-82-34615-00/01

156-83-34616-00/01

## **16 DATE OF REVISION OF THE TEXT**

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פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר ע"י משרד הבריאות בתאריך 02.2017, ועודכן בהתאם להוראות משרד הבריאות בתאריך 03.2020.