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. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Instruct patients to take the recommended dosage as directed, because overdosage has led to deaths *[see Overdosage (9)]*.

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 (14)*].

If a NINLARO 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 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/mm^3
- Platelet count should be at least 75,000/mm^3
- Non-hematologic toxicities should, at the healthcare provider'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 Dosage 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: Dosage Modifications Guidelines for NINLARO in Combination with Lenalidomide and Dexamethasone

Hematological Toxicities	**Recommended Actions**
Thrombocytopenia (Platelet Count)	
Platelet count less than 30,000/mm^3	• Withhold NINLARO and lenalidomide until platelet count is at least 30,000/mm^3. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume NINLARO at its most recent dose. • If platelet count falls to less than 30,000/mm^3 again, withhold NINLARO and lenalidomide until platelet count is at least 30,000/mm^3. • Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*

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

Neutropenia (Absolute Neutrophil Count)	
Absolute neutrophil count less than 500/mm^3	• Withhold NINLARO and lenalidomide until absolute neutrophil count is at least 500/mm^3. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume NINLARO at its most recent dose. • If absolute neutrophil count falls to less than 500/mm^3 again, withhold NINLARO and lenalidomide until absolute neutrophil count is at least 500/mm^3. • Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*
Non-Hematological Toxicities	**Recommended Actions**
Rash	
Grade† 2 or 3	• Withhold lenalidomide until rash recovers to Grade 1 or lower. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information. • If Grade 2 or 3 rash occurs again, withhold NINLARO and lenalidomide until rash recovers to Grade 1 or lower. • Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*
Grade 4	Discontinue treatment regimen.
Peripheral Neuropathy	
Grade 1 Peripheral Neuropathy with Pain or Grade 2 Peripheral Neuropathy	• Withhold NINLARO until peripheral neuropathy recovers to Grade 1 or lower without pain or patient's baseline. • Following recovery, resume NINLARO at its most recent dose.
Grade 2 Peripheral Neuropathy with Pain or Grade 3 Peripheral Neuropathy	• Withhold NINLARO. Toxicities should, at the healthcare provider's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming NINLARO. • Following recovery, resume NINLARO at the next lower dose.
Grade 4 Peripheral Neuropathy	Discontinue treatment regimen.
Other Non-Hematological Toxicities	
Other Grade 3 or 4 Non-Hematological Toxicities	• Withhold NINLARO. Toxicities should, at the healthcare provider's discretion, generally recover to patient's baseline condition or Grade 1 or lower prior to resuming NINLARO. • If attributable to NINLARO, resume NINLARO at the next lower dose following recovery.

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

†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 capsules:

- 4 mg ixazomib: Light orange gelatin capsule imprinted with “Takeda” on the cap and “4 mg” on the body in black ink.
- 3 mg ixazomib: Light grey gelatin capsule imprinted with “Takeda” on the cap and “3 mg” on the body in black ink.
- 2.3 mg ixazomib: Light pink gelatin capsule imprinted with “Takeda” on the cap and “2.3 mg” on the body in black ink.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 13.

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 *[see Adverse Reactions (6.1)]*. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. The rate of platelet transfusions was 10% in the NINLARO regimen and 7% 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 52% of patients in the NINLARO regimen and 43% in the placebo regimen, constipation in 35% and 28%, respectively, nausea in 32% and 23%, respectively, and vomiting in 26% and 13%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen *[see Adverse Reactions (6.1)]*. 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 16% in the placebo regimen) and Grade 2 (11% in the NINLARO regimen and 6% in the placebo regimen) *[see Adverse Reactions (6.1)]*. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens.

The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% 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 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. 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 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (17% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 6% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively*[see Adverse Reactions (6.1)]*. Peripheral edema resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. 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 27% of patients in the NINLARO regimen and 16% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen) *[see Adverse Reactions (6.1)]*. Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Serious adverse reactions of rash were reported in <1% of patients in the NINLARO regimen. 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)*].

Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal cases, have been reported with NINLARO *[see Adverse Reactions (6.1, 6.2)]*. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, discontinue NINLARO and manage as clinically indicated.

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 *[see Adverse Reactions (6.1)]*. 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 *[see Adverse Reactions (6.1)]*. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% 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 animal studies. 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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose *[see Drug Interactions (7.1) and Use in Specific Populations (8.1, 8.3)]*.

5.9 Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting

In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials *[see Clinical Studies (13.2)]*.

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359).

The most frequently reported adverse reactions (≥ 20% with a difference of ≥5% compared to placebo) in the NINLARO regimen were thrombocytopenia, neutropenia, diarrhea, constipation, peripheral neuropathy, nausea, peripheral edema, rash, vomiting, and bronchitis. Serious adverse reactions reported in ≥ 2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%) and bronchitis (2%). One or more of the three drugs was permanently discontinued in 4% of patients reporting peripheral neuropathy, 3% of patients reporting diarrhea and 2% of patients reporting thrombocytopenia. Permanent discontinuation of NINLARO due to an adverse reaction occurred in 10% of patients.

Table 4 summarizes the non-hematologic 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 ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

System Organ Class / Preferred Term	NINLARO + Lenalidomide and Dexamethasone N=361			Placebo + Lenalidomide and Dexamethasone N=359		
	%			%		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhea	52	10	0	43	3	0
Constipation	35	< 1	0	28	< 1	0
Nausea	32	2	0	23	0	0
Vomiting	26	1	0	13	<1	0
Nervous system disorders						
Peripheral neuropathies†	32	2	0	24	2	0
Musculoskeletal and connective tissue disorders						
Back pain*	27	<1	0	24	3	0
Infections and infestations						
Upper respiratory tract infection*	27	1	0	23	1	0
Bronchitis	22	2	0	17	2	<1
Skin and subcutaneous tissue disorders						
Rash†	27	3	0	16	2	0
General disorders and administration site conditions						
Edema peripheral	27	2	0	21	1	0

Note: Adverse reactions included as preferred terms are based on MedDRA version 23.0.

* At the time of the final analysis, these adverse reactions no longer met the criterion for a ≥ 5% difference

†Represents a pooling of preferred terms

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

Table 5: Thrombocytopenia and Neutropenia

	NINLARO + Lenalidomide and Dexamethasone N=361		Placebo + Lenalidomide and Dexamethasone N=359	
	%		%	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Thrombocytopenia	85	30	67	14
Neutropenia	74	34	70	37

Herpes Zoster

Herpes zoster was reported in 6% of patients in the NINLARO regimen and 3% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider'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 (10%).

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 38% in patients in the NINLARO regimen. The most common adverse reactions of the eyes were cataract (15%), conjunctivitis (9%), blurred vision (7%) and dry eye (6%).

Other Clinical Trials Experience

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

6.2 Post marketing Experience

The following adverse reactions have been identified during post-approval use of NINLARO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Angioedema

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis

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 [*see Clinical Pharmacology (11.1)*] and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. 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 pregnant women of the potential risk to a fetus.

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 (≥ 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 0.6 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

8.2 Lactation

Risk Summary

There are no data on the presence of ixazomib 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 of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential

NINLARO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating NINLARO.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the last dose. 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 *[see Drug Interactions (7.1)]*.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the last dose.

8.4 Pediatric Use

Safety and effectiveness of NINLARO 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

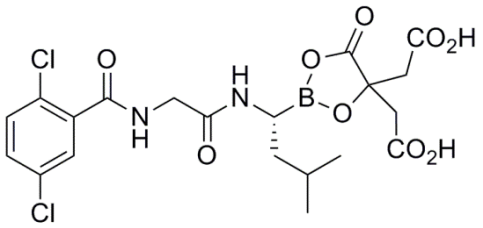
In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can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

9 OVERDOSAGE

Overdosage, including fatal overdosage, has been reported in patients taking NINLARO.
Manifestations of overdosage include adverse reactions reported at the recommended dosage *[see Dosage and Administration (2.1), Adverse Reactions (6.1)].* Serious adverse reactions reported with overdosage include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death.
In the event of an overdosage, monitor for adverse reactions and provide appropriate supportive care.
NINLARO is not dialyzable.

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-[(1*R*)-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}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 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 ≤ 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 ≥ 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 ≥ 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

13.1 Multiple Myeloma in Patients Who Have Received at Least One Prior Therapy

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 healthcare provider'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

	NINLARO + Lenalidomide and Dexamethasone (N = 360)	**Placebo + Lenalidomide and Dexamethasone (N = 362)**
Patient Characteristics		
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)
Disease Characteristics		
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)

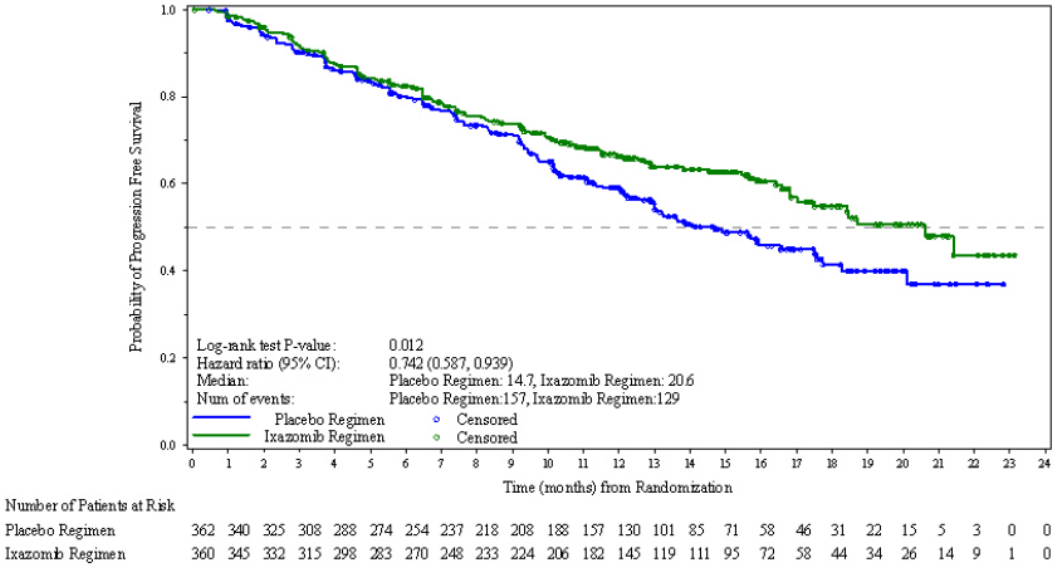
NE: Not evaluable.

*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.

†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 final analysis for OS at a median duration of follow up of approximately 85 months, median OS in the ITT population was 53.6 months for patients in the NINLARO regimen and 51.6 months for patients in the placebo regimen (HR = 0.94 [95% CI: 0.78, 1.13]).

13.2 Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting

In C16019 (NCT02181413), newly diagnosed multiple myeloma patients who underwent autologous stem cell transplantation, continued on maintenance therapy for 24 months. There were 27% (105/395) deaths in the NINLARO arm compared with 26% (69/261) in the placebo arm. The hazard ratio for overall survival was 1.008 (95% CI: 0.744 - 1.367).

In C16021 (NCT02312258), newly diagnosed multiple myeloma patients, not treated with a stem cell transplant who achieved a partial response or better, continued on maintenance therapy for 24 months. There were 30% (127/425) deaths in the NINLARO arm compared with 27% (76/281) in the placebo arm. The hazard ratio for overall survival was 1.136 (95% CI: 0.853 - 1.514).

NINLARO is not recommended for use in the maintenance setting for multiple myeloma outside of controlled clinical trials *[see Indications and Usage (1) and Warnings and Precautions (5.9)]*.

13.3 Lack of Efficacy in Patients with Newly Diagnosed Multiple Myeloma

Lack of efficacy in patients with newly diagnosed multiple myeloma was determined in a prospective randomized clinical trial.

In C16014 (NCT01850524), in newly diagnosed multiple myeloma patients, the study did not meet the prespecified primary endpoint for PFS. There were 136 (39%) deaths in the NINLARO, lenalidomide, and dexamethasone arm compared to 148 (42%) in the lenalidomide and dexamethasone arm. The hazard ratio for overall survival was 0.998 (95% CI: 0.79 - 1.261).

NINLARO is not recommended for use in combination with lenalidomide and dexamethasone in newly diagnosed multiple myeloma outside of controlled clinical trials *[see Indications and Usage (1)]*.

13 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

14 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NINLARO is supplied as follows:

Strength per Capsule	Capsule Description	Outer Carton	Blister Pack
4 mg	Light orange, size 3, imprinted with "Takeda" on the cap and "4 mg" on the body in black ink.	Three 4 mg single blister packs in a carton	Each blister has one 4 mg capsule
3 mg	Light grey, size 4, imprinted with "Takeda" on the cap and "3 mg" on the body in black ink.	Three 3 mg single blister packs in a carton	Each blister has one 3 mg capsule
2.3 mg	Light pink, size 4, imprinted with "Takeda" on the cap and "2.3 mg" on the body in black ink.	Three 2.3 mg single blister packs in a carton	Each blister has one 2.3 mg capsule

PVC-Aluminum/Aluminum blister strip containing three capsules, sealed inside a wallet pack.

One wallet pack is packaged in one carton.

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.

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.

Registration Holder and Importer's name and address:
Takeda Israel Ltd., 25 Efal St., Petach Tikva 4951125

Registration Numbers:
156-81-34609-00
156-82-34615-00
156-83-34616-00

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