NINLARO®
(ixazomib) capsules
4mg | 3mg | 2.3mg

DOSING GUIDE

Indication

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

Please see Important Safety Information within the Safety tab and accompanying NINLARO (ixazomib) full Prescribing Information.

The NINLARO® (ixazomib) regimen offers the convenience of oral administration

Dosing

- The recommended starting dose of NINLARO is 4 mg (one capsule) in combination with lenalidomide and dexamethasone*

Communicating with your patient

Tips and reminders have been included in this brochure to facilitate communication with patients. You can recognize them by their orange callout box.

Share the following information at the start of treatment to ensure patients and caregivers are well informed:

- Drug and indication
- Dose and dosing schedule
- Start date
- Handling instructions
- Administration and what to do if a dose is missed
- Food and drug interactions
- Side effects and management

Plan for individualized adherence strategies[1]

- Have patients build a routine and take medication during a certain activity every day
- Encourage patients to keep track of each dose by keeping a medication diary
- Help set alarms (eg, watches, smartphones, text/call reminders)

Treatment should be continued until disease progression or unacceptable toxicity

*A 3-mg starting dose is recommended for patients with moderate or severe hepatic impairment and patients with severe renal impairment or end-stage renal disease requiring dialysis. A 2.3-mg dose is also available for subsequent dose reductions due to adverse reactions (ARs).

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NINLARO® (ixazomib) capsules
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NINLARO® (ixazomib) is available in the following capsule strengths:

- **4 mg:** Light orange gelatin capsule imprinted with the Takeda logo on the cap and 4.0 mg on the body in black ink
- **3 mg:** Light gray gelatin capsule imprinted with the Takeda logo on the cap and 3.0 mg on the body in black ink
- **2.3 mg:** Light pink gelatin capsule imprinted with the Takeda logo on the cap and 2.3 mg on the body in black ink

Dosing schedule

- The recommended dosing schedule for each 28-day treatment cycle of:
  - — NINLARO is 4 mg (one capsule) administered orally once a week on days 1, 8, and 15
  - — Lenalidomide is 25 mg administered orally daily on days 1 through 21
  - — Dexamethasone is 40 mg administered orally on days 1, 8, 15, and 22

Dosing schedule

NINLARO (4 mg, 3 mg, 2.3 mg)

Lenalidomide (25 mg)

Dexamethasone (40 mg)

For more information on dosing administration requirements, see the next page.

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NINLARO® (ixazomib) dosing considerations

- NINLARO should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a 4-week cycle

NINLARO should not be taken with food. Food may interfere with the absorption of NINLARO, which may lower levels of the medication in the blood and possibly reduce effectiveness.

- NINLARO should be taken on an empty stomach or at least 1 hour before or at least 2 hours after food
- NINLARO should not be taken at the same time as dexamethasone because **dexamethasone should be taken with food**

- **No body surface area dosing is required**
- **NINLARO should be swallowed whole with water and should not be crushed, chewed, or opened**
- **If a NINLARO dose is delayed or missed, the dose should be taken only if the next scheduled dose is at least 72 hours away**
  - — 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
- **Antiviral prophylaxis should be considered in patients being treated with NINLARO to decrease the risk of herpes zoster reactivation**

Considerations prior to initiating a new cycle of therapy

- Absolute neutrophil count should be at least 1000/mm^3
- Platelet count should be at least 75,000/mm^3. Monitor platelet counts at least monthly during treatment with NINLARO
- Nonhematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or grade 1 or lower

Communication is key

- There's no such thing as overcommunicating
- To verify comprehension, have patients repeat information in their own words

Dose modification options are available if above administration guidelines are not met—refer to dose modifications on pages 13–17

Please see Important Safety Information within the Safety tab and accompanying NINLARO (ixazomib) full Prescribing Information.

NINLARO® (ixazomib) capsules 4mg | 3mg | 2.3mg

Storage

- NINLARO® (ixazomib) may be stored at room temperature. Do not store above 30°C (86°F). Do not freeze
- Store capsules in original packaging until immediately prior to use

Handling & Disposal

- NINLARO is cytotoxic. Capsules should not be opened, crushed, or chewed. Direct contact with the capsule contents should be avoided
- NINLARO is available in single dose packs (1 pill) and complete monthly dose packs (3 pills)
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Capsule breakage

- In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If skin contact occurs, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water

Capsule warnings

Capsule should not be crushed

Capsule should not be chewed

Capsule should not be opened

Capsule should not be removed from original packaging until time of consumption

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Nonhematologic ARs occurring in ≥5% of patients with a ≥5% difference between the NINLARO® (ixazomib) regimen* and the placebo regimen†

AR	NINLARO regimen (n=360)			Placebo regimen (n=360)			Difference
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Upper respiratory tract infection	**19%**	<1%	0	**14%**	<1%	0	**5%**
Peripheral neuropathies‡	**28%**	2%	0	**21%**	2%	0	**7%**
Diarrhea	**42%**	6%	0	**36%**	2%	0	**6%**
Constipation	**34%**	<1%	0	**25%**	<1%	0	**9%**
Nausea	**26%**	2%	0	**21%**	0	0	**5%**
Vomiting	**22%**	1%	0	**11%**	<1%	0	**11%**
Rash‡	**19%**	3%	0	**11%**	1%	0	**8%**
Back pain	**21%**	<1%	0	**16%**	3%	0	**5%**
Peripheral edema	**25%**	2%	0	**18%**	1%	0	**7%**

*NINLARO+lenalidomide+dexamethasone.
†Placebo+lenalidomide+dexamethasone.
‡Represents a pooling of preferred terms.

Additional safety information

- Serious ARs reported in ≥2% of patients included thrombocytopenia (2%) and diarrhea (2%)
- Incidence of thrombocytopenia in patients in the NINLARO and placebo regimens, respectively: all grades, 78% vs 54%; grades 3-4, 26% vs 11%
- Incidence of neutropenia in the NINLARO and placebo regimens, respectively: all grades, 67% vs 66%; grades 3-4, 26% vs 30%

Please see Important Safety Information within the Safety tab and accompanying NINLARO (ixazomib) full Prescribing Information.

Thrombocytopenia and neutropenia AR and laboratory data

	NINLARO® (ixazomib) regimen (n=360)		Placebo regimen (n=360)	
	n (%)		n (%)	
	ANY GRADE	GRADES 3-4	ANY GRADE	GRADES 3-4
Thrombocytopenia	281 (78)	93 (26)	196 (54)	39 (11)
Neutropenia	240 (67)	93 (26)	239 (66)	107 (30)

Represents pooled information.

- For each AR, 1 or more of the 3 drugs were discontinued in ≤1% of patients in the NINLARO regimen

Management of some ARs may require modification of the NINLARO dose

NINLARO dose modification schedule

4 mg 	Recommended starting dose
3 mg 	First dose reduction Recommended starting dose for patients with: • Moderate or severe hepatic impairment* • Severe renal impairment† • End-stage renal disease requiring dialysis
2.3 mg 	Second dose reduction
If toxicities continue	Discontinuation

Not actual capsule size.

- No dose adjustment is required for:
  - — Elderly patients
  - — Patients with mild to moderate renal impairment†
  - — Patients with mild hepatic impairment*
- NINLARO can be taken if patient is on dialysis

*Hepatic impairment: mild, total bilirubin ≤1.5 × ULN; moderate, total bilirubin >1.5-3 × ULN; severe, total bilirubin >3 × ULN.

†Renal impairment: mild to moderate, creatinine clearance ≥30 mL/min; severe, creatinine clearance <30 mL/min.

ULN=upper limit of normal.

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Dose modification guidelines for the NINLARO® (ixazomib) regimen

Hematologic toxicity Thrombocytopenia (platelet count)	Recommended action
Platelet count <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 <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*

Hematologic toxicity Neutropenia (absolute neutrophil count)	Recommended action
Absolute neutrophil count <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 <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*

*For additional occurrences, alternate dose modification of lenalidomide and NINLARO.
G-CSF=granulocyte-colony stimulating factor.

The first dose modification step for overlapping hematologic toxicities is to reduce the lenalidomide dose after withholding NINLARO and lenalidomide

- Refer to the lenalidomide Prescribing Information for the dose reduction steps for these toxicities

Please see Important Safety Information within the Safety tab and accompanying NINLARO (ixazomib) full Prescribing Information.

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Dose modifications guidelines for the NINLARO® (ixazomib) regimen (cont'd)

Nonhematologic toxicity	Recommended action
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 physician'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 nonhematologic toxicity	Recommended action
Other grade 3 or 4 nonhematologic toxicities	• 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 • If attributable to NINLARO, resume NINLARO at the next lower dose following recovery

Rash maculo-papular[2]
Grade 2: macules/papules covering 10%–30% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (ADL); rash covering >30% BSA with or without mild symptoms.
Grade 3: macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL.
Peripheral sensory neuropathy[2]
Grade 1: asymptomatic.
Grade 2: moderate symptoms; limiting instrumental ADL.
Grade 3: severe symptoms; limiting self-care ADL.
Grade 4: life-threatening consequences; urgent intervention indicated.

The first dose modification step for overlapping toxicities of rash is to withhold/reduce lenalidomide

*Grading based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
†For additional occurrences, alternate dose modification of lenalidomide and NINLARO.

Provide patients with close follow-up support

- Encourage patients to report any side effects as they occur so the appropriate management measures can be taken

Please see Important Safety Information within the Safety tab and accompanying NINLARO (ixazomib) full Prescribing Information.

For additional information regarding lenalidomide and dexamethasone, please see their Prescribing Information.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO® (ixazomib). During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.
- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the 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 severe symptoms.
- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, 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. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.
- **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.
- **Cutaneous Reactions:** Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. 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.
- **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.
- **Hepatotoxicity** has been reported with NINLARO. 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 during treatment and adjust dosing as needed.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO. Women using hormonal contraceptives should also use a barrier method of contraception.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

SPECIAL POPULATIONS

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
- **Lactation:** Advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

REFERENCES: 1. McCue DA, Lohr LK, Pick AM. Improving adherence to oral cancer therapy in clinical practice. *Pharmacotherapy*. 2014;34(5):481-494. **2.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published November 27, 2017.

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Please see accompanying NINLARO (ixazomib) full Prescribing Information.

NINLARO® (ixazomib): What you need to know

Dosing

- The recommended starting dose of NINLARO is 4 mg (one capsule) in combination with lenalidomide and dexamethasone
- NINLARO is available in 3 capsule strengths

Schedule

- NINLARO is taken once a week for the first 3 weeks of a 4-week cycle
- Treatment should be continued until disease progression or unacceptable toxicity

Indication

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.

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CONTACT US FOR ADDITIONAL INFORMATION

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