TREATMENT CONSIDERATIONS WITH NINLARO® (ixazomib)

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.

TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of the NINLARO regimen (ixazomib+lenalidomide+dexamethasone) vs the placebo regimen (placebo+lenalidomide+dexamethasone) until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. 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.

Please see Important Safety Information throughout and accompanying NINLARO (ixazomib) full Prescribing Information.

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

CONTENTS

INDICATION AND IMPORTANT SAFETY INFORMATION 1
CONTENTS PAGE 2
IMPORTANT SAFETY INFORMATION 3
IMPORTANT SAFETY INFORMATION: SPECIAL POPULATIONS 4
SELECTED SAFETY PROFILE 5
ADDITIONAL SAFETY INFORMATION 6
DISCONTINUATION RATES 7
COMMON SIDE EFFECTS AND MANAGEMENT 8
DOSING 9
CAPSULE STRENGTHS 10
DOSING CONSIDERATIONS 11
DOSING CONSIDERATIONS (cont'd) 12
DOSE MODIFICATION GUIDELINES 13
DOSE MODIFICATION GUIDELINES (cont'd) 14
PATIENT SUPPORT AND REFERENCES 15

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WARNINGS AND PRECAUTIONS (cont'd)

- **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO® (ixazomib). 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.

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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.

Contraception: Male and female patients of childbearing potential must use effective contraceptive measures during, and for 90 days following, treatment.

NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

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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.
AR=adverse reaction.

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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: any grade, 78% vs 54%; grades 3-4, 26% vs 11%
- Incidence of neutropenia in the NINLARO and placebo regimens, respectively: any grade, 67% vs 66%; grades 3-4, 26% vs 30%

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Discontinuation rates were comparable between the NINLARO® (ixazomib) and placebo regimens

Discontinuation rates of the entire regimen due to ARs

13% vs 11%

of the NINLARO and placebo regimens, respectively[2]

Dose tolerability

80%

of patients continued at the starting dose of NINLARO without dose reduction[2]

- For each adverse reaction, 1 or more of the 3 drugs were discontinued in ≤1% of patients in the NINLARO regimen
- The median time on therapy for patients in the NINLARO arm was 17 cycles compared with 15 cycles for patients in the placebo arm[1]
- The most common ARs (≥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 ARs reported in ≥2% of patients included thrombocytopenia (2%) and diarrhea (2%)

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Concomitant medications may be given for prophylaxis and/or management of symptoms

Condition	Prophylaxis/symptomatic	Consider*
GI toxicity: diarrhea[3,4]	Symptomatic	Antidiarrheal (eg, loperamide)
GI toxicity: nausea/vomiting[3,4]	Prophylaxis or symptomatic	Antiemetics, antinauseants (eg, ondansetron, metoclopramide)
Viral infection: herpes zoster (reactivation)[3,4]	Prophylaxis† or symptomatic	Antivirals
Rash[3,4]	Prophylaxis or symptomatic	Antihistamines (eg, cetirizine) or corticosteroids (oral or topical; eg, prednisone)

*The above medications and supportive therapies are examples of appropriate supportive care that was permitted in the phase 3 clinical trial.

†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%).

Encourage patients and caregivers to report any side effects early so appropriate management measures can be taken.

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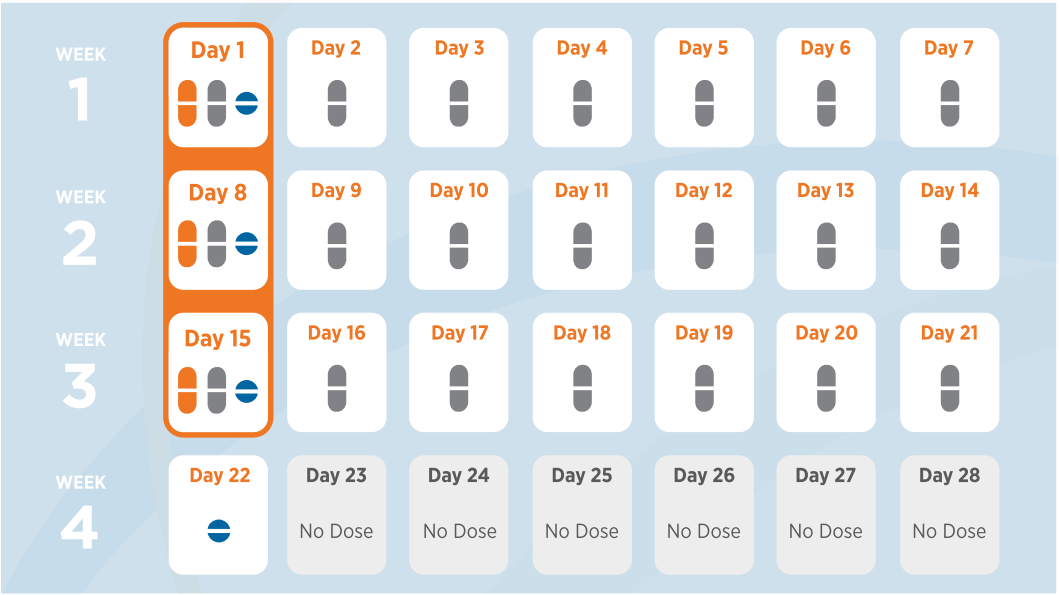
Dosing schedule



As the graphic shows,

NINLARO is administered orally on days 1, 8, and 15 of a 28-day cycle.

Lenalidomide is administered orally on days 1-21 of a 28-day cycle.

Dexamethasone is administered orally on days 1, 8, 15, and 22 of a 28-day cycle.

Please note that there is **NO DOSING** on days 23-28.

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

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 ARs.

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NINLARO is available in the following capsule strengths

4 mg

3 mg

2.3 mg

Not actual capsule size.

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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**

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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

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Hematologic toxicity	Recommended action
Thrombocytopenia (platelet count)	
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*
Neutropenia (absolute neutrophil count)	
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.

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

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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

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

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Visit www.Here2Assist.com or call 1-844-817-6468 for information on access, coverage, and support services.

REFERENCES: 1. Moreau P, Masszi T, Grzasko N, et al; for TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634. **2.** Data on File 117, Takeda Pharmaceuticals International Co. **3.** Kumar S, Moreau P, Hari P, et al. Management of adverse events associated with ixazomib plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma. *Br J Haematol*. 2017;178(4):571-582. **4.** Kumar SK, Vij R, Noga SJ, et al. Treating multiple myeloma patients with oral therapies. *Clin Lymphoma Myeloma Leuk*. 2017;17(5):243-251.

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