A GUIDE TO MANAGING ADVERSE REACTIONS
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 NINLARO (an oral proteasome inhibitor) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior lines of therapy.

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 occurred between Days 14-21 of each 28-day cycle and typically recovered to baseline by the start of the next cycle.

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

Please see Important Safety Information on pages 1-2 and accompanying full Prescribing Information.

WARNINGS AND PRECAUTIONS (CONTINUED)

- **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.
- **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	RENAL IMPAIRMENT	LACTATION
Reduce the starting dose of NINLARO to 3 mg in patients with moderate or severe hepatic impairment.	Reduce the starting dose of NINLARO to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis.	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 regimen* and the placebo regimen†

AR	NINLARO regimen (n=360)			Placebo+len+dex (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.
ARs=adverse reactions.

Serious ARs

- Serious ARs reported in ≥2% of patients in the NINLARO regimen included thrombocytopenia (2%) and diarrhea (2%)

Pooled hematologic adverse events and laboratory data

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

Thrombocytopenia followed a cyclical pattern, with platelet nadirs generally occurring between days 14-21 of a 28-day cycle and recovering to baseline by the start of the next cycle.

Additional Safety information

- NINLARO did not prolong the QTc interval at clinically relevant exposures
- Incidence of eye disorders§ with NINLARO vs placebo: all grades, 26% vs 16%; grade 3, 2% vs 1%, respectively
- The majority of peripheral neuropathy ARs were grade 1 (18% vs 14%, respectively)
  - Peripheral neuropathy grade 3 ARs were 2% in both regimens; no grade 4 or serious ARs reported

§Most commonly reported as blurred vision, dry eye, and conjunctivitis.

The NINLARO® (ixazomib) regimen represented a sustainable treatment for patients

Discontinuation rates of the full regimen due to ARs[1]

80% of patients continued at the 4-mg starting dose of NINLARO without dose reduction.[1]

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PREPARE PATIENTS FOR SIDE EFFECTS AND DOSING CONCERNS

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

Condition	Prophylaxis/symptomatic	Recommendation
GI toxicity: diarrhea[3]	Symptomatic	Antidiarrheal (eg, loperamide)
GI toxicity: nausea/vomiting[3]	Prophylaxis or symptomatic	Antiemetics, antinauseants (eg, ondansetron)
Viral infection: herpes zoster (reactivation)[4]	Prophylaxis or symptomatic	Direct-acting antivirals (eg, acyclovir, valacyclovir)
Rash[5]	Prophylaxis (subsequent cycles) or symptomatic	Antihistamines (eg, cetirizine) or corticosteroids (oral or topical; eg, prednisone, betamethasone)
Bacterial infection[6]	Prophylaxis or symptomatic	Antibacterials • Prophylaxis (eg, sulfonamides, trimethoprim) • Symptomatic (eg, beta-lactam antibacterials, penicillins)

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

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

DOSE MODIFICATION GUIDELINES FOR THE NINLARO® (ixazomib) REGIMEN

HEMATOLOGIC 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*
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*

NONHEMATOLOGIC 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 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 TOXICITIES	RECOMMENDED ACTIONS
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).
Grade 3: macules/papules covering >30% BSA with or without associated symptoms-limiting self-care ADL.

Peripheral sensory neuropathy[2]
Grade 1: asymptomatic; loss of deep tendon reflexes or paresthesia.
Grade 2: moderate symptoms; limiting instrumental ADL.
Grade 3: severe symptoms; limiting self-care ADL.
Grade 4: life-threatening consequences; urgent intervention indicated.

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

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

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AVAILABLE NINLARO® (ixazomib) STRENGTHS

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

*Hepatic impairment: moderate, bilirubin >1.5-3x ULN; severe, bilirubin >3x ULN.
†Severe renal impairment: Creatinine clearance <30 mL/min.

Please see section 2 (Dosing and Administration) of the NINLARO full Prescribing Information.

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4mg | 3mg | 2.3mg

Call 1-844-N1POINT (1-844-617-6468) for information on access, coverage, and support services.

References: 1. Data on File 117, Takeda Pharmaceuticals International Co. **2.** US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. Published June 14, 2010. **3.** Data on File 113, Takeda Pharmaceuticals International Co. **4.** Data on File 109, Takeda Pharmaceuticals International Co. **5.** Data on File 114, Takeda Pharmaceuticals International Co. **6.** Data on File 115, Takeda Pharmaceuticals International Co.

Please see attached full Prescribing Information above.

ONCOLOGY

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