

## 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 full Prescribing Information enclosed in the pocket.**

## NINLARO® (ixazomib) 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 gray 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

### NINLARO IS AVAILABLE IN THE FOLLOWING CAPSULE STRENGTHS:

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

### ► TREATMENT SHOULD BE CONTINUED UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY

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## DOSING SCHEDULE

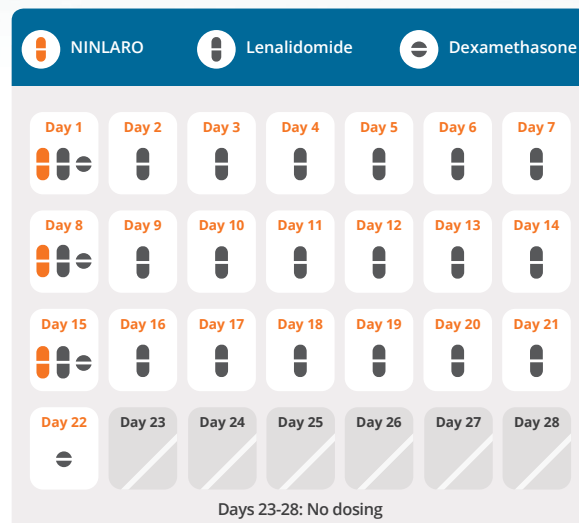
- The recommended starting dose for each 28-day treatment cycle of:
  - NINLARO® (ixazomib) is 4 mg (one capsule) administered orally once a week on days 1, 8, and 15
  - Lenalidomide is 25 mg administered orally daily on days 1 through 21<sup>1</sup>
  - Dexamethasone is 40 mg administered orally on days 1, 8, 15, and 22<sup>1</sup>
- NINLARO must be taken at least 1 hour before or at least 2 hours after food
- Dexamethasone should be taken with food
- NINLARO and dexamethasone should not be taken at the same time



### PLAN FOR INDIVIDUALIZED ADHERENCE STRATEGIES<sup>2</sup>

- 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)

## ▶ DOSING SCHEDULE



## IMPORTANT CONSIDERATIONS FOR NINLARO® (ixazomib) DOSAGE AND HANDLING

### DOSING CONSIDERATIONS

- NINLARO should be taken at the same time each week, at least 1 hour before or at least 2 hours after food
- If a dose of NINLARO is missed or delayed, it can be taken as long as the next 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 a missed dose
- NINLARO should be swallowed whole with a glass of water
- If a patient vomits after taking a dose, do not repeat the dose. Instead, continue at the time of the next scheduled dose

### ONGOING CONSIDERATION

- Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first 3 cycles

### CONSIDERATIONS PRIOR TO INITIATING A NEW CYCLE OF THERAPY

- Absolute neutrophil count should be  $\geq 1000/\text{mm}^3$
- Platelet count should be  $\geq 75,000/\text{mm}^3$
- Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or grade  $\leq 1$
- Consider prophylactic antivirals to prevent herpes zoster reactivation<sup>3</sup>



#### 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 CRITERIA ARE NOT MET—REFER TO DOSE MODIFICATIONS ON PAGES 13-17**

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## HANDLING

- NINLARO® (ixazomib) is cytotoxic. Direct contact with the capsule contents should be avoided
- Advise patients to store capsules in original packaging. Advise them not to remove the capsule until just prior to dosing
- NINLARO is available in single dose packs (1 pill) and complete monthly dose packs (3 pills)



### CONSIDERATIONS FOR 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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**NON-HEMATOLOGIC ADVERSE REACTIONS (ARs) OCCURRING IN ≥5% OF PATIENTS WITH A ≥5% DIFFERENCE BETWEEN THE NINLARO® (ixazomib) REGIMEN AND THE PLACEBO REGIMEN (ALL GRADES, GRADE 3, AND GRADE 4)**

	<b>NINLARO+ LENALIDOMIDE+DEXAMETHASONE (n=360)</b>			<b>Placebo+ LENALIDOMIDE+DEXAMETHASONE (n=360)</b>		
	ALL GRADES	GRADE 3	GRADE 4	ALL GRADES	GRADE 3	GRADE 4
<b>Infections and infestations</b>						
Upper respiratory tract infection	19%	<1%	0	14%	<1%	0
<b>Nervous system disorders</b>						
Peripheral neuropathies*	28%	2%	0	21%	2%	0
<b>Gastrointestinal disorders</b>						
Diarrhea	42%	6%	0	36%	2%	0
Constipation	34%	<1%	0	25%	<1%	0
Nausea	26%	2%	0	21%	0	0
Vomiting	22%	1%	0	11%	<1%	0
<b>Skin and subcutaneous tissue disorders</b>						
Rash*	19%	3%	0	11%	1%	0
<b>Musculoskeletal and connective tissue disorders</b>						
Back pain	21%	<1%	0	16%	3%	0
<b>General disorders and administration site conditions</b>						
Edema peripheral	25%	2%	0	18%	1%	0

\*Represents a pooling of preferred terms.

ADVERSE REACTIONS

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## THROMBOCYTOPENIA AND NEUTROPENIA ADVERSE EVENT AND LABORATORY DATA

	NINLARO + LENALIDOMIDE + DEXAMETHASONE (n=360)		Placebo + LENALIDOMIDE + DEXAMETHASONE (n=360)	
	n (%)		n (%)	
	ANY GRADE	GRADE 3-4	ANY GRADE	GRADE 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 adverse reaction, 1 or more of the 3 drugs was discontinued in ≤1% of patients in the NINLARO regimen

## MANAGEMENT OF SOME ARS MAY REQUIRE MODIFICATION OF THE NINLARO® (ixazomib) DOSE

NINLARO DOSE MODIFICATION SCHEDULE	
<b>4 mg</b> 	Recommended starting dose
<b>3 mg</b> 	First dose reduction  Recommended starting dose for patients with: <ul style="list-style-type: none"> <li>• Moderate or severe hepatic impairment</li> <li>• Severe renal impairment*</li> <li>• End-stage renal disease including dialysis</li> </ul>
<b>2.3 mg</b> 	Second dose reduction
<b>If toxicities continue</b>	Discontinuation

- No dose adjustment is required for:
  - Elderly patients
  - Patients with mild to moderate renal impairment<sup>†</sup>
  - Patients with mild hepatic impairment<sup>‡</sup>
- NINLARO can be taken if patient is on dialysis

\*Creatinine clearance <30 mL/min.

†Creatinine clearance ≥30 mL/min.

‡Total bilirubin ≤1.5 x the upper limit of normal (ULN).

DOSE  
MODIFICATION

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## THROMBOCYTOPENIA AND NEUTROPENIA ADVERSE EVENT AND LABORATORY DATA

	NINLARO + LENALIDOMIDE + DEXAMETHASONE (n=360)		Placebo + LENALIDOMIDE + DEXAMETHASONE (n=360)	
	n (%)		n (%)	
	ANY GRADE	GRADE 3-4	ANY GRADE	GRADE 3-4
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\*Creatinine clearance <30 mL/min.

<sup>†</sup>Creatinine clearance ≥30 mL/min.

<sup>‡</sup>Total bilirubin ≤1.5 x the upper limit of normal (ULN).

DOSE  
MODIFICATION

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## DOSE MODIFICATIONS GUIDELINES FOR NINLARO IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE

HEMATOLOGIC TOXICITIES	RECOMMENDED ACTIONS
<b>Thrombocytopenia (platelet count)</b>	
Platelet count less than 30,000/mm <sup>3</sup>	<ul style="list-style-type: none"> <li>Withhold NINLARO® (ixazomib) and lenalidomide until platelet count is at least 30,000/mm<sup>3</sup></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 30,000/mm<sup>3</sup> again, withhold NINLARO and lenalidomide until platelet count is at least 30,000/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>

► **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

HEMATOLOGIC TOXICITIES	RECOMMENDED ACTIONS
<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>

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

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## DOSE MODIFICATIONS GUIDELINES FOR NINLARO IN COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE (cont'd)

NONHEMATOLOGIC TOXICITIES	RECOMMENDED ACTIONS
<b>Rash</b>	
Grade* 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® (ixazomib) 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<sup>†</sup></li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>Discontinue treatment regimen</li> </ul>
<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	<ul style="list-style-type: none"> <li>Discontinue treatment regimen</li> </ul>

OTHER NONHEMATOLOGIC TOXICITIES	RECOMMENDED ACTIONS
Other grade 3 or 4 nonhematologic 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>

### ▶ THE FIRST DOSE MODIFICATION STEP FOR OVERLAPPING TOXICITIES OF RASH IS TO WITHHOLD/REDUCE LENALIDOMIDE

\*Grading based on National Cancer Institute Common Terminology Criteria Version 4.03.  
<sup>†</sup>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

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## 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.
- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of anti-diarrheal 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 maculopapular 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.

## WARNINGS AND PRECAUTIONS (continued)

- **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%).

## 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.

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

**REFERENCES:** 1. Data on File 108, Takeda Pharmaceuticals International Co. 2. McCue DA, Lohr LK, Pick AM. Improving adherence to oral cancer therapy in clinical practice. *Pharmacotherapy*. 2014;34(5): 481-494. 3. Data on File 109, Takeda Pharmaceuticals International Co.



Please see accompanying NINLARO full Prescribing Information enclosed in the pocket.

# 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

## STORAGE

- NINLARO may be stored at room temperature. Do not store above 30°C (86°F). Do not freeze
- Store capsules in the original packaging. Do not remove the capsule until just prior to dosing

## DISPOSAL

- Dispose of any unused medicinal product or waste in compliance with local regulations





## CONTACT US FOR ADDITIONAL INFORMATION

### Phone: 1-844-N1POINT

Select option 1 for medical information

Select option 2 for NINLARO 1Point



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