PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNINLARO™

ixazomib (as ixazomib citrate)

4 mg, 3 mg and 2.3 mg capsules

Antineoplastic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule 4 mg, 3 mg and 2.3 mg	Microcrystalline cellulose, magnesium stearate, talc, gelatin, titanium dioxide, yellow iron oxide, red iron oxide, shellac, propylene glycol, potassium hydroxide, black iron oxide *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

Geriatrics (≥ 65 years of age):

In studies of NINLARO™, there were no clinically significant differences in safety and efficacy between patients less than 65 years of age and patients 65 years of age or older (see **Special Populations**).

Pediatrics (< 18 years of age):

The safety and efficacy of NINLARO™ in children below 18 years of age have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

NINLARO™ should be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.

- Consult the product monographs for REVLIMID® (lenalidomide) and dexamethasone, which are administered in combination with NINLARO™, for additional health professional information.
- Prior to initiating a new cycle of therapy:

  Absolute neutrophil count should be ≥ 1,000/mm^3

  Platelet count should be ≥ 75,000/mm^3 (see **DOSAGE AND ADMINISTRATION**).
- Avoid direct contact with capsule contents because NINLARO™ may be harmful by inhalation, ingestion, or skin absorption. Do not crush, chew, or open capsules (see **SPECIAL HANDLING INSTRUCTIONS**).

General

Peripheral Edema

Peripheral edema has been reported with NINLARO™ (see **ADVERSE REACTIONS**). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO™ and placebo regimens, respectively. There were no Grade 4 or 5 events reported. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing for Grade 3 or 4 symptoms (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal

Diarrhea, vomiting, nausea and constipation have been reported with NINLARO™ (see **ADVERSE REACTIONS**). Medical management included dose modification, use of antidiarrheal and antiemetic medications, and supportive care. Adjust dosing for Grade 3 or 4 symptoms (see **DOSAGE AND ADMINISTRATION**).

Hematologic

Thrombocytopenia

Thrombocytopenia has been reported with NINLARO™ (see **ADVERSE REACTIONS**) 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. Thrombocytopenia (combined preferred terms of thrombocytopenia and platelet count decreased) was reported as an adverse event in 28% of

patients in the NINLARO™ regimen and 14% in the placebo regimen. The difference in frequency was across all grades, including Grade 3 and Grade 4 thrombocytopenia (13% and 5% of patients in the NINLARO™ and placebo regimens, respectively). Three percent of patients in the NINLARO™ regimen and 1% of patients in the placebo regimen had a platelet count $\leq 10{,}000/mm^3$ during treatment. Thrombocytopenia did not result in an increase in hemorrhagic events or platelet transfusions.

Platelet counts should be monitored at least monthly during NINLARO™ treatment. More frequent monitoring should be considered during the first three cycles. Thrombocytopenia should be managed with dose modifications (see **DOSAGE AND ADMINISTRATION**) and platelet transfusions as per standard medical guidelines.

Hepatic

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 and adjust dosing for Grade 3 or 4 symptoms (see **DOSAGE AND ADMINISTRATION***).*

Infections and Infestations

Herpes Zoster

Herpes zoster was reported in 4% of patients in the NINLARO™ regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the physician'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 (6%). Antiviral prophylaxis should be considered in patients being treated with NINLARO™ to decrease the risk of herpes zoster reactivation.

Neurologic

Peripheral neuropathy

Peripheral neuropathies have been reported with NINLARO™ (see **ADVERSE REACTIONS**). The majority of peripheral neuropathy adverse reactions were Grade 1 (18% and 14% in the NINLARO™ and placebo regimen, respectively) and Grade 2 (8% and 5% in the NINLARO™ and placebo regimen, respectively). Grade 3 peripheral neuropathy was reported at 2% in both regimens; there were no Grade 4 adverse reactions. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO™ and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). The overall incidence of peripheral neuropathy specifically with pain was 3% in the NINLARO™ regimen and 2% 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**).

Skin

Rash (representing a pooling of preferred terms) has been reported as an adverse event associated with NINLARO™. Grade 3 rash was reported in 3% of patients in the NINLARO™ regimen compared to 1% of patients in the placebo regimen, and there were no Grade 4 adverse events of rash across the Phase 3 study. The most common type of rash reported in both regimens included maculo-papular and macular rash. Across the NINLARO™ development program, serious cutaneous adverse events have been reported (see **ADVERSE REACTIONS**).

Rash should be managed with dose modification/discontinuation if Grade 2 or higher, and supportive care (see **DOSAGE AND ADMINISTRATION**).

Sexual Function/Reproduction

Fertility studies were not conducted with NINLARO™. There were no effects in reproductive organs in either males or females in nonclinical studies in rats and dogs (see **TOXICOLOGY**).

Special Populations

Pregnant Women: NINLARO™ can cause fetal harm when administered to a pregnant woman. There are no human data available regarding the potential effect of NINLARO™ on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in plasma exposures that were slightly higher than those observed in patients receiving the recommended dose (see **TOXICOLOGY**).

Advise women of the potential risk to a fetus. Women should not become pregnant while being treated with NINLARO™.

Male and female patients of child-bearing potential must use two effective contraceptive measures during and for 90 days following treatment. Since some oral contraceptive products may interact with dexamethasone, and NINLARO™ is administered with dexamethasone, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using oral hormonal contraceptives should also use a barrier method of contraception.

Nursing Women: It is not known whether ixazomib/metabolites are excreted in human milk. Many drugs are excreted in human milk and as a result, there could be a potential for adverse events in nursing infants. Advise women to discontinue nursing.

Pediatrics (< 18 years of age): The safety and efficacy of NINLARO™ in children below 18 years of age have not been established.

Geriatrics (≥ 65 years of age): No dose adjustment of NINLARO™ is required for patients over

65 years of age based on the results of a population PK analysis.

In studies of NINLARO™, there were no clinically significant differences in safety and efficacy between patients less than 65 years of age and patients 65 years of age or older.

Hepatic Impairment: No dose adjustment of NINLARO™ is required for patients with mild hepatic impairment. A lower starting dose of 3 mg is recommended for patients with moderate or severe hepatic impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment: No dose adjustment of NINLARO™ is required for patients with mild or moderate renal impairment. A lower starting dose of 3 mg is recommended for patients with severe renal impairment 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 **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Monitoring and Laboratory Tests

Platelet counts should be monitored at least monthly during NINLARO™ treatment. More frequent monitoring should be considered during the first three cycles.

Monitor hepatic enzymes regularly when NINLARO™ is administered in combination with lenalidomide and dexamethasone

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data was primarily from the Phase 3 clinical study in patients with relapsed and/or refractory multiple myeloma. The most frequently reported NINLARO™ adverse drug reactions (≥ 20%) were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse drug reactions reported in ≥ 2% of patients in the NINLARO™ regimen included thrombocytopenia (2%) and diarrhea (2%).

In the Phase 3 study, the median dose intensity for NINLARO™ and placebo was high and similar in the NINLARO™ and placebo regimens: 97.4% and 98.2%, respectively. Dose modifications in both regimens were more common in the first 6 cycles and decreased in frequency over time. Dose modifications included a dose reduction, a cycle delay or dosing delay within a cycle, dose being held, dose missed, or treatment discontinuation. Eighty percent of patients in the NINLARO™ regimen continued treatment at the starting dose of NINLARO™ without dose reduction. Further, the median dose intensity was high and similar in both the NINLARO™ and placebo regimens for lenalidomide: 93.8% and 95.6%, respectively, and for dexamethasone, 92.8% and 95.0%, respectively.

For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO™ regimen. The rates of discontinuation of the full study drug regimen due to a

treatment-emergent adverse event were 13% in the NINLARO™ regimen and 11% in the placebo regimen.

Across the NINLARO™ development program, the following serious cutaneous adverse events were reported: erythema multiforme, acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis and cutaneous vasculitis.

Across the NINLARO™ development program, the following serious adverse events for which causality has not been established were rarely reported: transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety population from the Phase 3, 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=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360). In the NINLARO™ and placebo regimens, the median treatment duration was 341 days and 334 days, respectively.

Adverse events of any type were reported with similar frequency between the NINLARO™ and placebo regimens (98% and 99%, respectively). In all patients, the worst toxicity grade was most often Grade 3 (49% NINLARO™ regimen and 43% placebo regimen). The frequency of Grade 4 (15% and 14%, respectively) and Grade 5 (4% and 5%, respectively) adverse events was similar between the regimens.

Table 1 summarizes the adverse events, regardless of causality, occurring in ≥ 10% of patients in either the NINLARO™ regimen or the placebo regimen.

Table 1 Adverse Events Occurring in ≥ 10% of Patients in Either the NINLARO™ Regimen or the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO™ + Lenalidomide and Dexamethasone N=360			Placebo + Lenalidomide and Dexamethasone N=360		
System Organ Class / Preferred Term	**N (%)**			**N (%)**		
	All	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Infections and infestations						
Nasopharyngitis	71 (20)	0	0	66 (18)	0	0
Upper respiratory tract infection	69 (19)	1 (< 1)	0	52 (14)	2 (< 1)	0
Bronchitis	45 (13)	0	0	44 (12)	6 (2)	0
Pneumonia	32 (9)	20 (6)	2 (<1)	39 (11)	24 (7)	4 (1)
Blood and lymphatic system disorders						
Neutropenia[a]	109 (30)	57 (16)	16 (4)	96 (27)	51 (14)	20 (6)
Thrombocytopenia[b]	99 (28)	37 (10)	25 (7)	50 (14)	16 (4)	11 (3)
Anaemia[c]	97 (27)	33 (9)	0	94 (26)	45 (13)	0
Metabolism and nutrition disorders						
Decreased appetite	46 (13)	4 (1)	0	33 (9)	4 (1)	0
Hypokalaemia	40 (11)	9 (3)	6 (2)	33 (9)	3 (<1)	1 (<1)
Psychiatric disorders						
Insomnia	70 (19)	7 (2)	0	90 (25)	9 (3)	0
Nervous system disorders						
Peripheral neuropathies[d]	100 (28)	7 (2)	0	77 (21)	7 (2)	0
Dizziness	48 (13)	2 (<1)	0	34 (9)	1 (<1)	0
Headache	38 (11)	1 (<1)	0	37 (10)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	49 (14)	0	0	54 (15)	0	0
Dyspnoea	32 (9)	2 (<1)	0	35 (10)	4 (1)	0
Gastrointestinal disorders						
Diarrhea	151 (42)	22 (6)	0	130 (36)	8 (2)	0
Constipation	122 (34)	1 (< 1)	0	90 (25)	1 (< 1)	0
Nausea	92 (26)	6 (2)	0	74 (21)	0	0
Vomiting	79 (22)	4 (1)	0	39 (11)	2 (< 1)	0
Skin and subcutaneous tissue disorders						
Rash[e]	68 (19)	9 (3)	0	38 (11)	5 (1)	0
Pruritus	36 (10)	1 (<1)	0	25 (7)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	74 (21)	2 (< 1)	0	57 (16)	9 (3)	0

Muscle spasms	63 (18)	0	0	91 (25)	2 (<1)	0
Pain in extremity	38 (11)	1 (<1)	0	30 (8)	2 (<1)	0
Arthralgia	37 (10)	5 (1)	0	34 (9)	1 (<1)	0
General disorders and administration site conditions						
Fatigue	102 (28)	12 (3)	0	95 (26)	9 (3)	0
Edema peripheral	91 (25)	8 (2)	0	66 (18)	4 (1)	0
Asthenia	54 (15)	7 (2)	0	54 (15)	3 (<1)	0
Pyrexia	46 (13)	3 (<1)	0	69 (19)	5 (1)	0

Note: Adverse events included as preferred terms are based on MedDRA version 16.0.

(a) Neutropenia and neutrophil count decreased were combined to determine frequency of neutropenia.
(b)Thrombocytopenia and platelet count decreased were combined to determine frequency of thrombocytopenia.
(c) Anaemia and haemoglobin decreased were combined to determine frequency of anaemia.
(d) Neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and peripheral sensorimotor neuropathy were combined to determine frequency of peripheral neuropathy.
(e) MedDRA HLT 'Rashes, eruptions and exanthems NEC' was used to determine frequency of rash.

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO™ regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO™ regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO™ regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO™ regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO™ regimen and 1% in the placebo regimen.

DRUG INTERACTIONS

Overview

At clinically relevant ixazomib concentrations, in vitro studies indicate that no specific CYP isozyme predominantly contributes to ixazomib metabolism and non-CYP proteins contribute to overall metabolism. At concentrations exceeding those observed clinically, ixazomib was metabolized in vitro by multiple CYP isoforms (see ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics). Co-administration of NINLARO™ with strong CYP3A inducers is not recommended. The potential for ixazomib to produce clinically relevant drug-drug interactions via CYP isozyme induction or inhibition is low. Ixazomib is unlikely to cause or be susceptible to drug-drug interactions with substrates or inhibitors of clinically relevant drug transporters.

Drug-Drug Interactions

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%. Co-administration of strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's wort) with NINLARO™ is not recommended.

Strong CYP3A Inhibitors

Co-administration of NINLARO™ with clarithromycin did not result in a clinically meaningful change in the systemic exposure of ixazomib. Ixazomib C_{max} was decreased by 4% and AUC was increased by 11%. No dose modification is required for NINLARO™ with co-administration of strong CYP3A inhibitors.

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 the results of a population PK analysis. No dose modification is required for NINLARO™ with co-administration of strong CYP1A2 inhibitors.

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 and 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.

Drug-Food Interactions

Administration of NINLARO™ with a high-fat meal decreased ixazomib $AUC_{0\text{-}216h}$ by 28% and C_{max} by 69%, and delayed the time to the peak plasma concentration (T_{max}) from 1 hour to 4 hours, compared with administration after an overnight fast. Therefore, NINLARO™ should be taken at least one hour before or at least two hours after food.

Drug-Herb Interactions

Interactions with herbal products have not been established. Co-administration of St. John's wort (a strong CYP3A inducer) with NINLARO™ should be avoided.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies on the effects on the ability to drive or use machines have been performed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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. NINLARO™ should be taken at least one hour before or at least two hours after food (see **ACTION AND CLINICAL PHARMACOLOGY**). The capsule should be swallowed whole with water. The capsule should not be crushed, chewed or opened. Direct contact with capsule contents should be avoided as NINLARO™ may be harmful by inhalation, ingestion, or skin absorption (see **SPECIAL HANDLING INSTRUCTIONS**).

Recommended Dose and Dosage Adjustment

NINLARO™ in combination with lenalidomide and dexamethasone

The recommended starting dose of NINLARO™ is 4 mg (one capsule) 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 2 Dosing Schedule: 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 respective product monographs.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be ≥ 1,000/mm^3
- Platelet count should be ≥ 75,000/mm^3
- Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1

Treatment should be continued until disease progression or unacceptable toxicity.

Dose Modifications

The NINLARO™ dose reduction steps are presented in Table 3 and the dose modification guidelines are provided in Table 4.

Table 3 NINLARO™ Dose Reduction Steps

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.

An alternating dose modification approach is recommended for NINLARO™ and lenalidomide for overlapping toxicities of thrombocytopenia, neutropenia, and rash as described in Table 4. Refer to the lenalidomide product monograph for dose modification guidelines if dose modification is needed for lenalidomide.

Table 4 Dose Modifications Guidelines for NINLARO™ in Combination with Lenalidomide and Dexamethasone

Hematological Toxicities	**Recommended Actions**
Thrombocytopenia (Platelet Count)	
Platelet count < 30,000/mm^3	• Withhold NINLARO™ and lenalidomide until platelet count ≥ 30,000/mm^3. • Following recovery, resume lenalidomide at the next lower dose according to its product monograph 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 ≥ 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 product monograph 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 Rash	• Withhold lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, refer to the lenalidomide product monograph for dose modification guidelines. • If Grade 2 or 3 rash occurs again, withhold NINLARO™ and lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, resume NINLARO™ at the next lower dose and refer to the lenalidomide product monograph for dose modification guidelines. *
Grade 4 Rash	Discontinue the NINLARO™ regimen.
Peripheral Neuropathy	
Grade 1 Peripheral Neuropathy with Pain or Grade 2 Peripheral Neuropathy	• Withhold NINLARO™ until peripheral neuropathy recovers to ≤ Grade 1 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 prior to resuming NINLARO™. • Following recovery, resume NINLARO™ at the next lower dose.
Grade 4 Peripheral Neuropathy	Discontinue the NINLARO™ regimen.
Other Non-hematological Toxicities	
Other Grade 3 or 4 Non-Hematological Toxicities	• Withhold NINLARO™. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming NINLARO™. • If attributable to NINLARO™, resume NINLARO™ at the next lower dose following recovery or discontinue NINLARO™.

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

†Grading based on National Cancer Institute Common Terminology Criteria (CTCAE) Version 4.03

Special Populations

Hepatic Impairment

No dose adjustment of NINLARO™ is required for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1-1.5 x ULN and any AST) based on the results of a population pharmacokinetic (PK) analysis. A lower starting dose of 3 mg is recommended for patients with moderate (total bilirubin > 1.5-3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment based on the results of a PK study [see **ACTION AND CLINICAL PHARMACOLOGY**].

Renal Impairment

No dose adjustment of NINLARO™ is required for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on the results of a population PK analysis. A lower starting dose of 3 mg is recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease (ESRD) requiring dialysis based on the results of a PK study. NINLARO™ is not dialyzable and therefore can be administered without regard to the timing of dialysis [see **ACTION AND CLINICAL PHARMACOLOGY**].

Refer to the lenalidomide product monograph for dosing recommendations in patients with renal impairment.

Missed Dose

In the event that 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 a missed dose.

If a patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Based on limited data, the following adverse events were reported with overdose: syncope, polyneuropathy, neuralgia, convulsion, AST increased, peripheral neuropathy, and hypotension. There is no known specific antidote for ixazomib overdose. In the event of an overdose, monitor the patient for adverse reactions (see **ADVERSE REACTIONS**) and provide appropriate supportive care.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NINLARO™ (ixazomib) is an antineoplastic agent for oral use. Ixazomib citrate, a prodrug, is the drug substance that rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib.

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 several tumor cell types in vitro. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. In vivo, ixazomib demonstrated antitumor activity in various tumor xenograft models, including models of multiple myeloma.

In vitro, ixazomib inhibited proliferation of multiple myeloma cells co-cultured with bone marrow stromal cells. Ixazomib demonstrated an anti-angiogenic effect in an in vitro capillary tube formation assay.

Pharmacodynamics

Cardiac Electrophysiology

NINLARO™ does not prolong the QTc interval at clinically relevant exposures based on the results of a pharmacokinetic-pharmacodynamic analysis of data from 245 patients. There was no discernible relationship between ixazomib concentration and the RR interval.

Pharmacokinetics

Absorption: After oral administration, peak plasma concentrations of ixazomib were achieved at approximately one hour after dosing. The mean absolute oral bioavailability is 58% based on a population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 – 10.6 mg. The C_{max} and $AUC_{0\text{-}168h}$ in plasma and whole blood following once weekly oral administration of ixazomib 4 mg on Days 1, 8, and 15 in patients are shown in

Table 5 below.

Administration with a high-fat meal decreased ixazomib $AUC_{0\text{-}216h}$ by 28% and C_{max} by 69% compared with administration after an overnight fast. In addition, administration with food delayed the time to the peak plasma concentration (T_{max}) from 1 hour to 4 hours.

Table 5 Pharmacokinetic Parameters of Ixazomib After Day 15 Administration in Patients

Matrix	C_{max} (ng/mL)	AUC_{0-168h} (ng•h/mL)
Plasma	40.7 (66)	990 (42)
Whole Blood	125 (17)	9780 (20)

Values are presented as geometric mean (% coefficient of variation)

Distribution: Ixazomib is 99% bound to plasma proteins, primarily to serum albumin. Ixazomib distributes into red blood cells with a blood-to-plasma AUC ratio of 10 (see Table 5 above). The steady-state volume of distribution is 543 L based on a population PK analysis.

Elimination: Ixazomib exhibits a multi-exponential disposition profile. Based on a population PK analysis, systemic clearance (CL) was approximately 1.86 L/h with inter-individual variability of 44%. The terminal half-life ($t_{1/2}$) of ixazomib was 9.5 days. Approximately 2-fold accumulation in AUC was observed with weekly oral dosing on Day 15.

Metabolism: After oral administration of a single radiolabeled dose of 4.1 mg to 5 patients with advanced cancer, 70% of total drug-related material in plasma was accounted for by ixazomib. 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 indicate that no specific CYP isozyme predominantly contributes to ixazomib metabolism and non-CYP proteins contribute to overall metabolism. At concentrations exceeding those observed clinically, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) 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 over 35 days post dose. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

Special Populations and Conditions

Age, Gender, Race: There was no clinically meaningful effect of age (23-91 years), sex, body surface area (1.2-2.7 m^2), or race on the clearance of ixazomib based on the results of a population PK analysis. Mean $AUC_{0-\infty}$ was 35% higher in Asian patients than White patients.

Hepatic Impairment: The PK of ixazomib is 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 the results of a 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=10) or severe hepatic impairment at 1.5 mg (total bilirubin > 3 x ULN, N=11). Dose-normalized mean AUC was 20% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function.

Renal Impairment: The PK of ixazomib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on the results of a 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=15), severe renal impairment (creatinine clearance < 30 mL/min, N=10), 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.

STORAGE AND STABILITY

Store at 15°-30°C. Do not freeze.

Store capsules in original packaging until immediately prior to use.

SPECIAL HANDLING INSTRUCTIONS

NINLARO™ is cytotoxic. Capsules should not be opened or crushed. Direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid raising dust and wear gloves and protective clothing during clean-up. If contact occurs, wash thoroughly with soap and water.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NINLARO™ is supplied as capsules as follows:

4 mg: Light orange, marked “Takeda” on the cap and “4.0 mg” on the body with black ink

3 mg: Light grey, marked “Takeda” on the cap and “3.0 mg” on the body with black ink

2.3 mg: Light pink, marked “Takeda” on the cap and “2.3 mg” on the body with black ink

Each NINLARO™ capsule contains 5.7 mg, 4.3 mg, or 3.3 mg of ixazomib citrate which is equivalent to 4 mg, 3 mg, or 2.3 mg, respectively, of ixazomib and the following inactive ingredients: microcrystalline cellulose, magnesium stearate, and talc. In addition, the capsule shell contains the following inactive ingredients: gelatin, titanium dioxide, red and yellow oxide

(4 mg), black oxide (3 mg), red iron oxide (2.3 mg). The printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

NINLARO™ capsules are supplied as a multipack containing three capsules. Each multipack comprises of 3 cartons, each containing 1 capsule in a single blister pack. Capsules are individually packaged in a PVC-Aluminum/Aluminum blister.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

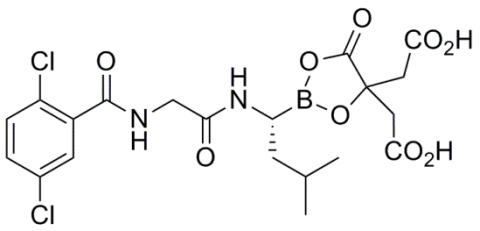
Drug Substance

Proper name: Ixazomib citrate

Chemical name: 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo-

Molecular formula and molecular mass: $C_{20}H_{23}BCl_2N_2O_9$
517.12

Structural formula:



Physicochemical properties: Ixazomib citrate has one chiral center and has been unambiguously determined to be 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.

CLINICAL TRIALS

Study C16010

Study demographics and trial design

The efficacy and safety of NINLARO™ in combination with lenalidomide and dexamethasone was evaluated in a randomized, double-blind, placebo-controlled, multicenter Phase 3 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 at any line were excluded from the study. For the purposes of this study, refractory disease was defined as disease progression on treatment or progression within 60 days after the last dose of lenalidomide or a proteasome inhibitor.

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 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). Patients enrolled in the trial had multiple myeloma that was measurable by paraprotein in the serum, urine, or via free light chain measurements.

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. Some patients with renal impairment received a reduced starting dose of lenalidomide. 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)**
Median age in years (range)	66 (38, 91)	66 (30, 89)
Gender (%) Male/ Female	58/42	56/44
Age Group (% [≤ 65/ > 65-≤ 75/ > 75 years])	47/40/13	49/35/17
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)
Type of myeloma (%) IgG/ IgA/ light chain	55/21/20	55/13/25
Free light chain-measurable only disease n (%)	43 (12)	44 (12)
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	212 (59)	213 (59)
2 or 3	148 (41)	149 (41)
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 (%)		
Any proteasome inhibitor†	249 (69)	253 (70)
Bortezomib containing	248 (69)	250 (69)
Carfilzomib containing	1 (<1)	4 (1)
Any immunomodulatory agent (IMiD)†	193 (54)	204 (56)
Thalidomide containing	157 (44)	170 (47)
Lenalidomide containing	44 (12)	44 (12)
Melphalan containing	293 (81)	291 (80)
Stem cell transplant	212 (59)	199 (55)
Cytogenetics‡		
High risk (deletion (del) 17, t(4:14) and/or t(14:16))	75 (21)	62 (17)
deletion (del) 17	36 (10)	33 (9)
Standard risk	199 (61)	216 (65)
Corrected calcium (mmol/L) median (min, max)	2.328 (1.87, 4.43)	2.324 (1.95, 3.45)
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)
Hemoglobin g/L median (min, max)	116 (68, 170)	115 (71, 167)
Lytic bone disease present at study	254 (71)	249 (69)

entry		

*A line of therapy was defined as 1 or more cycles of a planned treatment program.
**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.
†Subject counts once for each type of treatment.
‡One hundred seventy patients did not have cytogenetics results available for analysis.

The primary endpoint was 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. Confirmation of progressive disease was required. Progression and disease response were assessed every four weeks until disease progression. Overall survival (OS) and OS in patients harboring del(17) were key secondary endpoints. Other secondary endpoints included determination of overall response rate; duration of response; time to response; PFS in high-risk populations according to cytogenetics; and comparison of change in global health status, functioning, and symptoms measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Multiple Myeloma Module (MY-20).

There were two analyses for PFS and four planned for OS. The test for PFS was statistically significant at the first analysis thus it became the only analysis for statistical testing purposes. As a result, the study continued in a double-blind fashion with a non-inferential second analysis of PFS. Two interim analyses of overall survival have been conducted to date. If the test for OS was statistically significant, the key secondary endpoint of OS in patients harboring del(17) was to be assessed. All other analyses (except primary and key secondary endpoints) were conducted without adjustments for multiplicity.

Study results

At the first analysis for PFS (median follow up of 14.7 months and median number of cycles of 13), the NINLARO™ regimen demonstrated a statistically significant improvement in median PFS of approximately 6 months when compared to the placebo regimen in the intent-to-treat (ITT) population. PFS results are summarized in Table 7.

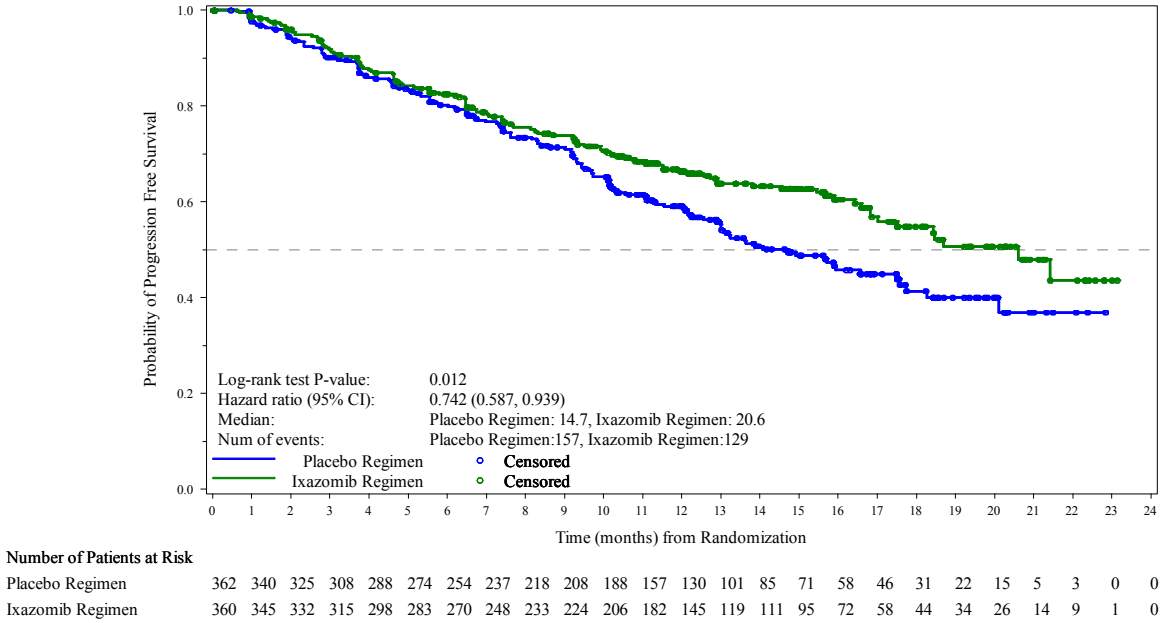
Table 7 Progression-Free Survival Results

	NINLARO™ + Lenalidomide and Dexamethasone (N = 360)	Placebo + Lenalidomide and Dexamethasone (N = 362)
Events, n (%)	129 (36)	157 (43)
Median (months) (95% CI)	20.6 (17.0, NE*)	14.7 (12.9, 17.6)
p-value**	0.012†	
Hazard Ratio‡ (95% CI)	0.74 (0.59, 0.94)	

*Not estimable
** P-value is based on the stratified log-rank test.
† Compared with the O'Brien-Fleming boundary of 0.02268.

‡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.

Figure 1 Kaplan-Meier Plot of Progression-Free Survival in the Intent to Treat Population



Number of Patients at Risk

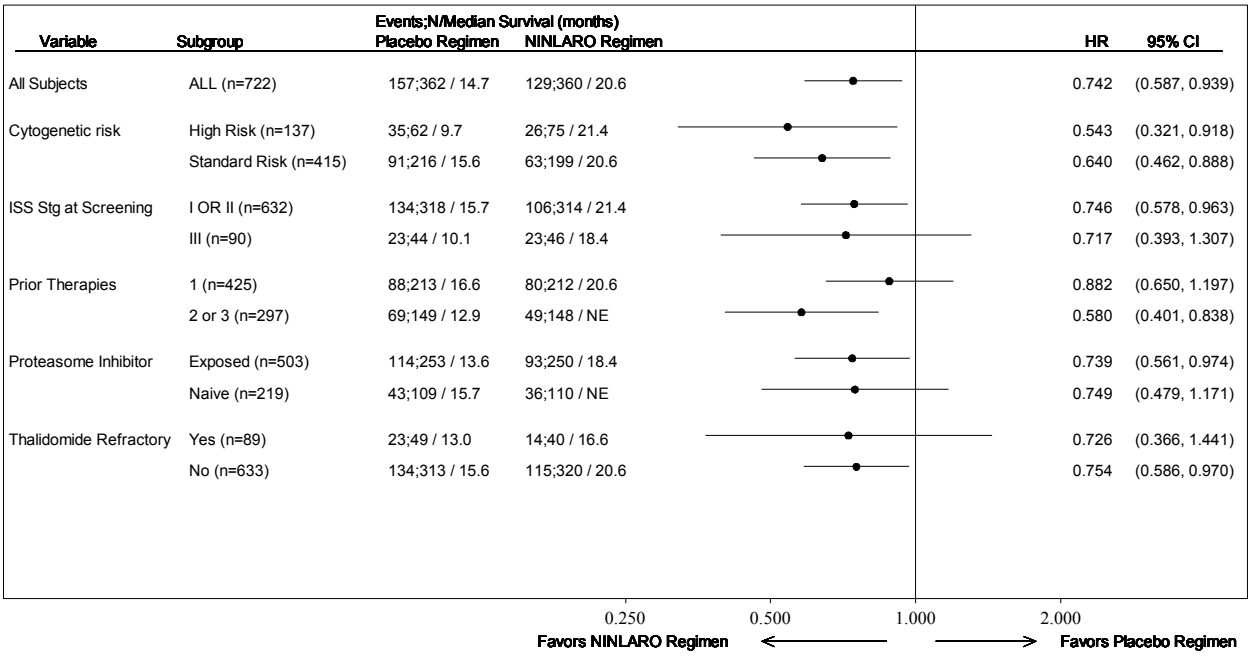
Placebo Regimen	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0
Ixazomib Regimen	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0

A non-inferential second 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 the NINLARO™ regimen versus the placebo regimen, and estimated median PFS was 20 months in the NINLARO™ regimen and 15.9 months in the placebo regimen. At the same time, a planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the NINLARO™ regimen and 90 deaths in the placebo regimen. An OS benefit was not demonstrated.

A pre-specified subgroup analysis for PFS was conducted in patients whose myeloma harbored high risk cytogenetic abnormalities, which included: del(17); translocation of chromosomes 4 and 14 (t[4:14]); and/or translocation of chromosomes 14 and 16 (t[14:16]. The hazard ratio was 0.54, with a nominal p-value=0.02. Median PFS was 21.4 months in the NINLARO™ regimen compared to 9.7 months in the placebo regimen.

Improvement in PFS with the addition of NINLARO™ to lenalidomide, and dexamethasone was observed across subgroup populations, including those defined by stratification factors, cytogenetics (high risk or standard risk), and thalidomide refractoriness (yes or no); see Figure 2 below.

Figure 2 Forest Plot of Progression-Free Survival in Subgroups



The improvement in PFS in the NINLARO™ regimen was supported by improvements in overall response rate. Response rates are summarized in Table 8.

Table 8 Response Data

	NINLARO™ + Lenalidomide and Dexamethasone (N = 360)	**Placebo + Lenalidomide and Dexamethasone (N = 362)**
Overall Response Rate (ORR)*, n (%) (Independent Review)	282 (78.3)	259 (71.5)
Complete Response (CR) + Very Good Partial Response (VGPR), n (%)	173 (48.1)	141 (39)
Response Category, n (%)		
CR	42 (11.7)	24 (6.6)
VGPR	131 (36.4)	117 (32.3)
Partial Response (PR)	109 (30.3)	118 (32.6)
Time to Response, months		
Median	1.1	1.9
Duration of Response†, months		
Median	20.5	15.0

*ORR = CR+PR +VGPR

†Based on responders in the response-evaluable population

In the Phase 3 study, the addition of NINLARO™ to lenalidomide and dexamethasone did not appear to have a negative impact on patient-reported outcomes. Quality of life was maintained during treatment and was similar in both regimens. There was a trend for better physical

functioning, emotional functioning, and fatigue scores for the NINLARO™ regimen compared with the placebo regimen, while diarrhea appeared to worsen in the NINLARO™ regimen in later cycles.

TOXICOLOGY

Carcinogenesis and Mutagenesis

Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay) nor was it clastogenic in a bone marrow micronucleus assay in mice. Ixazomib was considered positive in an in vitro clastogenicity test in human peripheral blood lymphocytes. However, ixazomib was negative for inducing DNA damage in the glandular stomach and liver in an in vivo comet assay in mice. Therefore, the weight of evidence supports that ixazomib does not present a genotoxic risk. No carcinogenicity studies have been performed with ixazomib.

Reproductive and Developmental Toxicity

Developmental toxicity studies in rats and rabbits did not show direct embryo-fetal toxicity below maternally toxic doses of ixazomib. In pregnant rat (0.6 mg/kg; $AUC_{0\text{-}72h}$=1081 ng hr/mL) and rabbit (1.0 mg/kg; $AUC_{0\text{-}72h}$=1340 ng hr/mL) dose range-finding studies, there were decreases in fetal weights, a trend towards decreased fetal viability, and/or increased post-implantation losses; however, these findings were not clearly reproduced in definitive studies, and were only observed at maternally toxic doses (0.6 mg/kg in rats, ≥0.25 mg/kg in rabbits) that caused decreased body weight and/or food consumption. In the definitive rabbit study, increases in fetal skeletal variations/abnormalities (caudal vertebrae, number of lumbar vertebrae and full supernumerary ribs) were observed at doses ≥ 0.3 mg/kg ($AUC_{0\text{-}72h}$=792 ng hr/mL), which were also associated with maternal toxicity. A dose of 0.1 mg/kg ($AUC_{0\text{-}72h}$=497 ng hr/mL) did not result in maternal toxicity or cause embryo-fetal effects.

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.

Animal Toxicology

In multi-cycle general toxicity studies conducted in rats and dogs, the principal target organs included the gastrointestinal (GI) tract, lymphoid tissues, and the nervous system.

GI findings included emesis and/or diarrhea increases in leukocyte parameters and microscopic changes (inflammation, epithelial hyperplasia, neutrophilic infiltration, single cell necrosis, congestion, hemorrhage, and/or erosion/ulceration). GI effects were observed at doses ≥0.2 mg/kg in rats (≥0.45 times human exposure based on plasma $AUC_{0\text{-}168h}$ in the 6-month rat study) and at ≥0.1 mg/kg in dogs (≥1.8 times human exposure based on plasma $AUC_{0\text{-}168h}$ in the 9-month dog study).

Lymphoid system toxicity was characterized by lymphoid depletion/necrosis (including bone marrow), neutrophilic infiltration, and single cell necrosis at doses ≥0.2 mg/kg in rats (≥0.45

times human exposure based on plasma $AUC_{0\text{-}168h}$) and at doses ≥0.1 mg/kg in dogs (≥1.8 times human exposure based on plasma $AUC_{0\text{-}168h}$).

Nervous system effects were primarily seen in dogs at oral doses ≥ 0.1 mg/kg ($AUC_{0\text{-}168h}$=1940 ng hr/mL) and included microscopic findings of minimal to mild neuronal degeneration of the sympathetic, dorsal root, peripheral autonomic (salivary gland), and end organ ganglia, and minimal secondary axonal/nerve fiber degeneration of the peripheral nerves and ascending tracts in the dorsal columns of the spinal cord. In the 9-month study (10 cycles) in dogs where the dosing regimen mimics the clinical regimen (28-day cycle), microscopic neuronal effects were generally minimal in nature at 0.2 mg/kg ($AUC_{0\text{-}168h}$= 3900 ng hr/mL; 3.6 times human exposure).

The majority of target organ findings demonstrated partial to full recovery following discontinuation of treatment, with the exception of neuronal findings in the lumbar dorsal root ganglion and dorsal column. The absence of ongoing neuronal degeneration in the peripheral ganglia and presence of only secondary degenerative changes in the nerve fibers and axons is consistent with lack of persistent toxicity.

In tissue distribution studies in rats, ixazomib did not result in excessive individual tissue exposure. The levels in the brain and spinal cord, in addition to the eye lens, had the lowest levels.

Based on the hERG assay, ixazomib weakly inhibits the potassium ion channel. The safety pharmacology study in conscious dogs demonstrated no effects of ixazomib on cardiovascular function at the highest dose tested (0.3 mg/kg).

REFERENCES

1. Kumar SK, Bensinger WI, Zimmerman TM et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014;124:1047-1055.

2. Kumar SK, Berdeja JG, Niesvizky R et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol. 2014;15:1503-1512.

3. Richardson PG, Baz R, Wang M et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. Blood 2014;124:1038-1046.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NINLARO™
ixazomib (as ixazomib citrate) capsules

Read this carefully before you start taking NINLARO™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NINLARO™.

Serious Warnings and Precautions

NINLARO™ should be prescribed and managed by a doctor experienced in the use of anticancer drugs.

- NINLARO™ is used together with two other drugs called REVLIMID® and dexamethasone. You should read the patient medication information leaflet for REVLIMID® and ask your healthcare professional for further information on their proper use and side effects.
- Before starting a new cycle of treatment with NINLARO™, your healthcare professional will do blood tests to check if you have enough white blood cells and platelets.
- Avoid direct contact with the capsule contents. Do not crush, chew, or open the NINLARO™ capsule.

What is NINLARO™ used for?
NINLARO™ is used together with REVLIMID® and dexamethasone, to treat adults with a type of cancer of the bone marrow called multiple myeloma. This is a cancer of the plasma cells (a type of white blood cell that produces antibodies). NINLARO™ is used in patients who have received at least one prior multiple myeloma treatment.

How does NINLARO™ work?
NINLARO™ is a proteasome inhibitor. Proteasomes play an important role in cells by breaking down unwanted proteins. NINLARO™ blocks proteasomes from working and causes a build-up of proteins in cells. This can cause cell death, especially in multiple myeloma cells because they are more likely to contain a higher amount of abnormal proteins.

What are the ingredients in NINLARO™?
Medicinal ingredients: ixazomib (as ixazomib citrate)

Non-medicinal ingredients: Black iron oxide (present in 3 mg capsules), gelatin, magnesium stearate, microcrystalline cellulose, potassium hydroxide, propylene glycol, red iron oxide (present in 2.3 mg and 4 mg capsules), shellac, talc, titanium dioxide, yellow iron oxide (present in 4 mg capsules)

NINLARO™ comes in the following dosage forms:
Capsules, 2.3 mg, 3 mg and 4 mg

Do not use NINLARO™ if:
- you are allergic to ixazomib or any of the other ingredients contained in NINLARO™ or the components of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NINLARO™. Talk about any health conditions or problems you may have, including if you:

- have a history of bleeding
- have persistent nausea, vomiting, constipation and/or diarrhea
- have or have had liver problems
- have or have had kidney problems
- are pregnant, think you may be pregnant, or plan to become pregnant. NINLARO™ can harm your unborn baby.
    - You should not become pregnant while being treated with NINLARO™.
    - If you are a woman who is able to become pregnant, you must use two forms of effective birth control during

treatment and for up to three months (90 days) after your last dose of NINLARO™. If using oral hormonal contraceptives (for example, the pill), an additional barrier method of contraception (for example, diaphragm or condom) must be used.

- If you are a man with a female partner who is able to become pregnant, you must use two forms of effective birth control during treatment and for up to three months (90 days) after your last dose of NINLARO™.
- Talk to your healthcare professional about birth control methods that may be right for you.
- Tell your healthcare professional right away if you or your partner becomes pregnant while you are receiving NINLARO™.

- are breastfeeding or plan to breastfeed. It is not known if ixazomib passes into breast milk. You and your healthcare professional should decide if you will take NINLARO™ or breastfeed. You should not do both.

Other warnings you should know about:

Infections

NINLARO™ may increase your risk of developing a painful skin rash with blisters on a small area of skin on one side of your face or body (shingles). Your doctor may give you antiviral drugs to decrease your risk of developing shingles.

Liver Problems

During treatment with NINLARO™, your healthcare professional will do blood tests to make sure your liver is working properly.

Children and Adolescents
NINLARO™ has not been studied in children less than 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NINLARO™:

- an antibiotic used to treat bacterial infections (rifampin)
- medicines used to prevent seizures or to treat epilepsy, or medicines used to treat a painful condition of the face called trigeminal neuralgia (carbamazepine and phenytoin)
- an herbal medicine used for depression (St. John's wort)

How to take NINLARO™:

Usual adult dose:

- Take NINLARO™ exactly as your healthcare professional tells you to take it. Do not change your dose or stop taking NINLARO™ without talking to your healthcare professional first.
- NINLARO™ is taken in "cycles". Each cycle lasts 4 weeks (28 days).
  - The usual dose of NINLARO™ is 1 capsule taken by mouth 1 time each week, on the same day of the week for the first 3 weeks of each cycle. Once a week on Days 1, 8, and 15 of a 28-day treatment cycle.
  - Take each dose of NINLARO™ at about the same time of day.
  - Take REVLIMID® and dexamethasone exactly as your healthcare professional tells you to.
  - Take REVLIMID® daily on Days 1-21 of a 28-day treatment cycle.
  - Take dexamethasone on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

Dosing Schedule: NINLARO™ taken with REVLIMID® 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™	✔		✔		✔			
REVLIMID®	✔	✔ Daily	✔	✔ Daily	✔	✔ Daily		
Dexamethasone	✔		✔		✔		✔	

- Take NINLARO™ at least 1 hour before or at least 2 hours after food. On the days that you take both NINLARO™ and dexamethasone, do not take NINLARO™ and dexamethasone at the same time. Take dexamethasone with food.
- Swallow NINLARO™ capsules whole with water. Do not crush, chew or open the capsule.
- Avoid direct contact with the capsule contents. If the capsule breaks, avoid spreading the capsule contents and wear gloves and protective clothing during clean-up. If you accidentally get powder from the NINLARO™ capsule on your skin, wash the area well with soap and water. If you accidentally get powder from the NINLARO™ capsule in your eyes, flush your eyes well with water.
- Most patients will receive treatment until their disease gets worse. NINLARO™ treatment may also be stopped if you experience side effects that cannot be managed.

Overdose:

If you think you have taken too much NINLARO™, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of NINLARO™, or if you are late taking a dose, take the dose as long as the next scheduled dose is more than 3 days (72 hours) away. Do not take a missed dose if it is within 3 days (72 hours) of your next scheduled dose. Do not take a double dose to make up for a missed dose.

If you vomit after taking a dose of NINLARO™, do not repeat the dose. Take your next scheduled dose of NINLARO™ on the next scheduled day and time.

What are possible side effects from using NINLARO™?

These are not all the possible side effects you may feel when taking NINLARO™. Tell your healthcare professional if any of the side effects listed bothers you or does not go away. If you experience any troublesome symptom or side effect not listed here, contact your healthcare professional.

Side effects affecting more than 1 in 10 people (≥10%):

- diarrhea
- nausea
- vomiting
- constipation
- low white blood cell counts (shown in blood tests)
- low platelet counts (shown in blood tests)
- low red blood cells (shown in blood tests)
- numbness, tingling, burning sensation, or pain of your hands or feet, weakness in your arms or legs

- feeling tired or weak
- swelling of your arms, hands, legs or feet, sudden weight gain
- fever
- back pain, pain in your arms or legs, joint pain
- muscle spasms or muscle cramps
- skin rash
- itchy skin
- cold or cold-like symptoms, inflammation of nasal passages
- bronchitis with cough, wheezing, or difficulty breathing
- pneumonia with cough, fever, chills
- decreased appetite
- low blood levels of potassium (shown in blood tests)
- trouble sleeping
- dizziness
- headache
- cough
- feeling short of breath

Side effects affecting up to 1 in 10 people (≥1% and <10%):

- blurred vision, dry eyes, whites of your eyes look red or pink

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
VERY COMMON Nose bleeds, bleeding from gums or other sites, abnormal bleeding, or easy bruising/low platelets	√	
Fever/low white blood cell counts	√	
Tiredness/low red blood cell counts	√	
Diarrhea	√	
Nausea	√	
Vomiting	√	
Constipation	√	
Numbness, tingling, burning sensation, or pain in hands or feet, weakness in arms or legs/nerve problems	√	

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
Swelling of arms, hands, legs, ankles, or feet, sudden weight gain/water retention	√	
Red rash across face and/or body	√	
Cough, fever, chills/pneumonia	√	
COMMON Painful blisters on a small area of skin on one side of face or body/shingles	√	
Yellowing of skin and eyes, stomach pain or swelling, nausea or vomiting/liver problems	√	
RARE Red to purple bumps on skin or rash with skin peeling and mouth sores	√	
Muscle weakness, loss of feelings of the toes and feet or loss of leg movement	√	
Changes in vision, changes in mental status, or seizures	√	
Dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances/rapid death of cancer cells	√	
Fatigue, fever, bruising, nose bleeds, decreased urination/ rare blood condition resulting from blood clots	√	

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store NINLARO™ at 15-30°C.

Do not freeze.

Store capsules in original packaging until immediately prior to use. Keep out of reach and sight of children.

If you want more information about NINLARO™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website http://www.takedacanada.com/, or by calling 1-866-295-4636.

This leaflet was prepared by Takeda Canada Inc., Oakville, Ontario L6M 4X8

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