AUSTRALIAN PRODUCT INFORMATION

NINLARO® (IXAZOMIB CITRATE)

1 NAME OF THE MEDICINE

Ixazomib citrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

NINLARO oral hard capsules contain 5.7 mg, 4.3 mg or 3.3 mg of ixazomib citrate equivalent to 4 mg, 3 mg or 2.3 mg of ixazomib, respectively.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Hard capsule. NINLARO is available in the following strengths:

4 mg: Light orange gelatin capsule imprinted with the Takeda logo on the cap and 4 mg on the body, in black ink

3 mg: Light grey gelatin capsule imprinted with the Takeda logo on the cap and 3 mg on the body, in black ink

2.3 mg: Light pink gelatin capsule imprinted with the Takeda logo on the cap and 2.3 mg on the body, in black ink

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and monitored under the supervision of a physician experienced in the management of multiple myeloma.

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 to 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 1 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 the respective Product Information documents.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be ≥ $1x10^9$/L
- Platelet count should be ≥ $75x10^9$/L
- Non-haematologic 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.

Delayed or missed doses

In the event that a NINLARO dose is delayed or missed, the dose should be taken only if the next scheduled dose is ≥ 72 h away. A missed dose should not be taken within 72 h 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.

Dose modifications

The NINLARO dose reduction steps are presented in Table 2 and the dose modification guidelines are provided in Table 3.

Table 2 NINLARO Dose Reduction Steps due to Adverse Reactions

Recommended starting dose*	First reduction to	Second reduction to	Discontinue
4 mg	3 mg	2.3 mg	

*Recommended lower dose of one 3 mg capsule in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease (ESRD) requiring dialysis.

An alternating dose modification approach is recommended for NINLARO and lenalidomide for overlapping toxicities of thrombocytopenia and rash. For these toxicities, the first dose modification step is to withhold/reduce lenalidomide. Refer to the lenalidomide Product Information, 4.2 Dose and Method of Administration, for the dose reduction steps for these toxicities and for neutropenia.

Table 3 Dose Modifications Guidelines for NINLARO in Combination with Lenalidomide and Dexamethasone

Haematological Toxicities	**Recommended Actions**
Thrombocytopenia (Platelet Count)	
Platelet count < $30x10^9$/L	• Withhold NINLARO and lenalidomide until platelet count ≥ $30x10^9$/L. • Following recovery, resume lenalidomide at the next lower dose according to its Product Information and resume NINLARO at its most recent dose. • If platelet count falls to < $30x10^9$/L again, withhold NINLARO and lenalidomide until platelet count ≥ $30x10^9$/L. • 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 $0.5x10^9$/L	• Withhold NINLARO and lenalidomide until absolute neutrophil count ≥ $0.5x10^9$/L. 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 < $0.5x10^9$/L again, withhold NINLARO and lenalidomide until absolute neutrophil count ≥ $0.5x10^9$/L. • Following recovery, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose.*
Non-Haematological Toxicities	**Recommended Actions**
Rash	
Grade† 2 or 3	• Withhold lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, resume lenalidomide at the next lower dose according to its Product Information. • 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 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 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 treatment regimen.
Other Non-Haematological Toxicities	
Other Grade 3 or 4 Non- Haematological 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 ixazomib, resume ixazomib at the next lower dose following recovery.

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

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

Concomitant medicinal products

Antiviral prophylaxis should be considered in patients being treated with ixazomib to decrease the risk of herpes zoster reactivation. Patients included in studies with NINLARO who received antiviral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receive prophylaxis (see 4.8 Adverse Effects).

Special Patient Populations

Elderly

No dose adjustment of NINLARO is required for patients over 65 years of age based on the results of a population pharmacokinetic (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.

Paediatric Population

The safety and efficacy of NINLARO in children below 18 years of age have not been established. No data are available.

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 PK analysis. A lower dose of one 3 mg capsule 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 5.2 Pharmacokinetic Properties, Special Populations).

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 dose of one 3 mg capsule 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 dialysable and therefore can be administered without regard to the timing of dialysis (see 5.2 Pharmacokinetic Properties, Special Populations).

Refer to the lenalidomide Product Information for dosing recommendations in patients with renal impairment.

Method of administration

Oral Use

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 1 h before or at least 2 h after food. The capsule should be swallowed whole with water. The capsule should not be crushed, chewed, or opened.

Handling

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the Product Information for these products for respective contraindications.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Thrombocytopenia

Thrombocytopenia has been reported with NINLARO 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 (see 4.8 Adverse Effects). Two percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ $10x10^9$/L during treatment. Less than 1% of patients in both regimens had a platelet count ≤ $5x10^9$/L during treatment. Thrombocytopenia resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. The incidence of hemorrhagic events was similar in the NINLARO (20%) and placebo (19%) regimens. The rate of platelet transfusions was also similar in the NINLARO (8%) and placebo regimen (6%).

Platelet counts should be monitored at least monthly during NINLARO treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide Product Information. Thrombocytopenia can be managed with dose modifications (see 4.2 Dose and Method of Administration) and platelet transfusions as per standard medical guidelines.

Gastrointestinal Toxicities

Diarrhoea, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antidiarrhoeal and antiemetic medications, and supportive care (see 4.8 Adverse Effects). Diarrhoea resulted in discontinuation of one or more of the three drugs in 2% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. The dose should be adjusted for severe (Grade 3–4) symptoms (see 4.8 Adverse Effects and 4.2 Dose and Method of Administration).

Use in the elderly

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 4.2 Dose and Method of Administration).

Paediatric use

The safety and efficacy of NINLARO in children below 18 years of age have not been established. No data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of Other Drugs on NINLARO

Strong CYP3A Inducers

Co-administration of NINLARO with rifampicin decreased ixazomib C_{max} by 54% and AUC by 74%.

Co-administration of strong CYP3A inducers (such as rifampicin, 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.

Effect of NINLARO on Other Drugs

NINLARO is not expected to produce drug-drug interactions via CYP inhibition or induction. 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.

Transporter-Based Interactions

NINLARO is not expected to cause transporter-mediated drug-drug interactions. Ixazomib is a low affinity substrate of P-glycoprotein (P-gp). Ixazomib is not a substrate of BCRP, MRP2, hepatic OATPs or NTCP. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, organic cation transporter (OCT)2, organic anion transporter (OAT)1, OAT3, MATE1, or MATE2-K.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been conducted with ixazomib.

Use in pregnancy (Category C)

Women should avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus.

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; however, embryo-fetal studies in animals have demonstrated that ixazomib has the potential to cause embryo-fetal lethality.

Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. When NINLARO is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using oral hormonal contraceptives should additionally use a barrier method of contraception.

In an embryofetal development study in pregnant rabbits there were increases in fetal skeletal variations/abnormalities (fused caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses ≥ 0.3 mg/kg/ 3 days. Exposures in the rabbit at 0.3 mg/kg/3 days were 1.5 times (based on AUC) or 0.4 times (based on C_{max}) the clinical exposure. Additionally, embryofetal lethality (increased postimplantation loss) was observed at 1 mg/kg/3 days in rabbits and at 0.6 mg/kg/3 days in rats in dose range finding studies. Exposures in rats at the dose of 0.6 mg/kg/ 3 days were 2 times (based on AUC) or 1.3 times (based on C_{max}) the clinical exposure.

Use in lactation

It is not known whether NINLARO/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Breast-feeding should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of ixazomib on the ability to drive or operate machinery. Fatigue and dizziness have been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience any of these symptoms.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

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=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359).

Summary of the safety profile

The most frequently reported adverse reactions (≥ 20%) across 361 patients treated within the NINLARO regimen and 359 within the placebo regimen in the pivotal clinical trial were diarrhoea (45% vs. 39%), constipation (35% vs. 26%), thrombocytopenia (31% vs. 16%), peripheral neuropathy (27% vs. 22%), nausea (29% vs. 22%), peripheral oedema (28% vs. 20%), vomiting (23% vs. 11%), back pain (24% vs. 17%) and upper respiratory tract infection (23% vs. 19%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2% in both regimens) and diarrhoea (2% and <1% in the NINLARO and placebo regimens, respectively).

Tabulated list of adverse reactions

Table 4 summarizes the adverse reactions occurring in at least 5% of patients with at least a 5% difference between the NINLARO regimen and the placebo regimen. The adverse reactions listed in

Table 4 are considered to be ADRs with a plausible connection with NINLARO.

Table 4 Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO + Len Dex N=361			Placebo+LenDex N=359		
System Organ Class / Preferred Term	**N (%)**			**N (%)**		
	All	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Thrombocytopenia[a]	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Nervous system disorders						
Peripheral neuropathies[b]	97 (27)	9 (2)	0	78 (22)	6 (2)	0
Gastrointestinal disorders						
Diarrhoea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Constipation	126 (35)	1 (<1)	0	94 (26)	1 (<1)	0
Nausea	104 (29)	6 (2)	0	79 (22)	0	0
Vomiting	84 (23)	4 (1)	0	42 (12)	2 (<1)	0
Skin and subcutaneous tissue disorders						
Rash[c]	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Musculoskeletal and connective tissue disorders						
Back pain	87 (24)	3 (<1)	0	62 (17)	9 (3)	0
General disorders and administration site conditions						
Oedema peripheral	101 (28)	8 (2)	0	73 (20)	4 (1)	0

[a] Thrombocytopenia and platelet count decreased were combined to determine frequency of thrombocytopenia.
[b] Neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and peripheral sensorimotor neuropathy were combined to determine frequency of peripheral neuropathy.
[c] The MedDRA HLT 'Rashes, eruptions and exanthems NEC' was used to determine the frequency of rash.

Description of selected adverse reactions

Thrombocytopenia and Gastrointestinal Toxicities are described in detail under the section PRECAUTIONS.

Peripheral neuropathy

The majority of peripheral neuropathy adverse reactions were Grade 1 and Grade 2. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions. The most commonly reported reaction was peripheral sensory neuropathy (19% and 15% 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 2% of patients in the NINLARO regimen and <1% of patients in the placebo regimen.

Rash

Rash occurred in 20% of patients in the NINLARO regimen compared to 13% of patients in the placebo regimen. The majority of the rash events were Grade 1 or Grade 2. Grade 3 rash was reported in 2% of patients in both the NINLARO regimen and placebo regimens and there were no Grade 4 adverse reactions of rash across the Phase 3 study. Serious adverse reactions of rash were reported in <1% of patients in both regimens. The most common type of rash reported in both regimens was maculo papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in ≤ 1% of patients in both regimens.

Dermal events have been reported with lenalidomide and dexamethasone.

Peripheral Oedema

Peripheral oedema was reported in 28% and 20% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral oedema adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 peripheral oedema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral oedema reported. There were no discontinuations reported due to peripheral oedema.

Herpes Zoster

Herpes zoster was reported in 5% 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 (8%).

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 32% in patients in the NINLARO regimen and 23% of patients in the placebo regimen. The most common adverse events were cataract (8% in the NINLARO regimen and 10% in the placebo regimen), blurred vision (7% in the NINLARO regimen and 4% in the placebo regimen), dry eye (5% in the NINLARO regimen and 2% in the placebo regimen), and conjunctivitis (7% in the NINLARO regimen and 2% in the placebo regimen). Grade 3 adverse events were reported in 4% of patients in both regimens.

Deaths

The frequency of on-study deaths in the Phase 3 Study was 15 (4%) in the NINLARO regimen and 23 (6%) in the placebo regimen. The incidence of deaths in the integrated safety analysis which includes different patient populations (N=990) was low (4%) and generally similar to that of the NINLARO regimen in the Phase 3 Study (4%).

Other Adverse Events

Outside of the Phase 3 study, the following serious adverse events for which causality has not been established were rarely reported: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumour lysis syndrome and thrombotic thrombocytopenic purpura.

Post-Marketing

Clinically significant adverse drug reactions are listed here if they have not been reported above.

Blood and lymphatic system disorders: thrombotic microangiopathy

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose has been reported in patients taking NINLARO. Symptoms of overdose are generally consistent with the known risks of NINLARO (see 4.8 Adverse Effects). Reports of accidental overdose have been associated with serious adverse events, such as severe nausea, aspiration pneumonia, multiple organ failure and death.

There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient closely for adverse reactions and provide appropriate supportive care.

Healthcare providers should instruct patients and care givers that only one dose of NINLARO should be taken at a time, and only at the prescribed interval (one capsule, once a week, on days 1, 8, and 15 of every 28-day cycle). The importance of carefully following all dosage instructions should be discussed with patients starting treatment.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ixazomib is an oral, selective and 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 tumour cell types *in vitro*. Ixazomib demonstrated *in vitro* cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. *In vivo*, ixazomib demonstrated antitumour activity in various tumour xenograft models, including models of multiple myeloma.

Ixazomib also disrupts the bone marrow microenvironment. *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. Ixazomib promoted osteoblastogenesis and osteoblast activity and inhibited osteoclastogenesis and osteoclast resorption *in vitro*. Additionally, ixazomib prevented bone loss in an *in vivo* mouse model of multiple myeloma.

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. At the 4 mg dose, mean change from baseline in QTcF is estimated to be 0.07 ms (90% CI; 0.22, 0.36) from the model based analysis.

There was no discernible relationship between ixazomib concentration and the RR interval suggesting no clinically meaningful effect of NINLARO on heart rate.

Clinical trials

The efficacy and safety of NINLARO in combination with lenalidomide and dexamethasone was evaluated in an international randomized, double-blind, placebo-controlled, multicenter Phase 3 superiority study in patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy. 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 and whose disease was refractory, including primary refractory (i.e., never responded to prior therapy), had relapsed after prior therapy, or had relapsed and was refractory to any prior line of therapy. Patients that changed therapies prior to disease progression were also

enrolled, as well as those with controlled cardiovascular conditions. Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide Product Information. Concomitant medications, such as antiemetic, antiviral, and antihistamine medications were given to patients at the physician's discretion as prophylaxis and/or management of symptoms.

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. Patients with renal impairment received a starting dose of lenalidomide according to its Product Information. Treatment continued until disease progression or unacceptable toxicities.

Table 5 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 5 Baseline Patient and Disease Characteristics

	NINLARO + Lenalidomide and Dexamethasone (N = 360)	Placebo + Lenalidomide and Dexamethasone (N = 362)
Patient Characteristics		
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	2 (<1)	6 (2)
ECOG performance status, n (%)		
0 or 1	336 (93)	334 (92)
2	18 (5)	24 (7)
Creatinine clearance, n (%)		
< 30 mL/min	5 (1)	5 (1)
30-59 mL/min	75 (21)	95 (26)
≥ 60 mL/min	281 (78)	261 (72)
Disease Characteristics		
Type of myeloma (%) IgG/ IgA/ free light chain	55/21/20	55/13/25
Myeloma ISS stage, n (%)		
Stage I or II	314 (87)	318 (88)
Stage III	46 (13)	44 (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)

	NINLARO + Lenalidomide and Dexamethasone (N = 360)	Placebo + Lenalidomide and Dexamethasone (N = 362)
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)
del(17)	36 (10)	33 (9)
Non-high risk	285 (79)	300 (83)
Lytic bone disease present at study entry	254 (71)	249 (69)

* 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.

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. Response was assessed every 4 weeks until disease progression. At the first pre-specified analysis (median follow up of 14.7 months and median number of cycles of 13), the NINLARO regimen demonstrated significantly superior results with an improvement in median PFS of approximately 6 months. At this analysis, patients receiving the NINLARO regimen lived significantly longer without their disease worsening compared to patients in the placebo regimen. PFS results are summarized in Table 6.

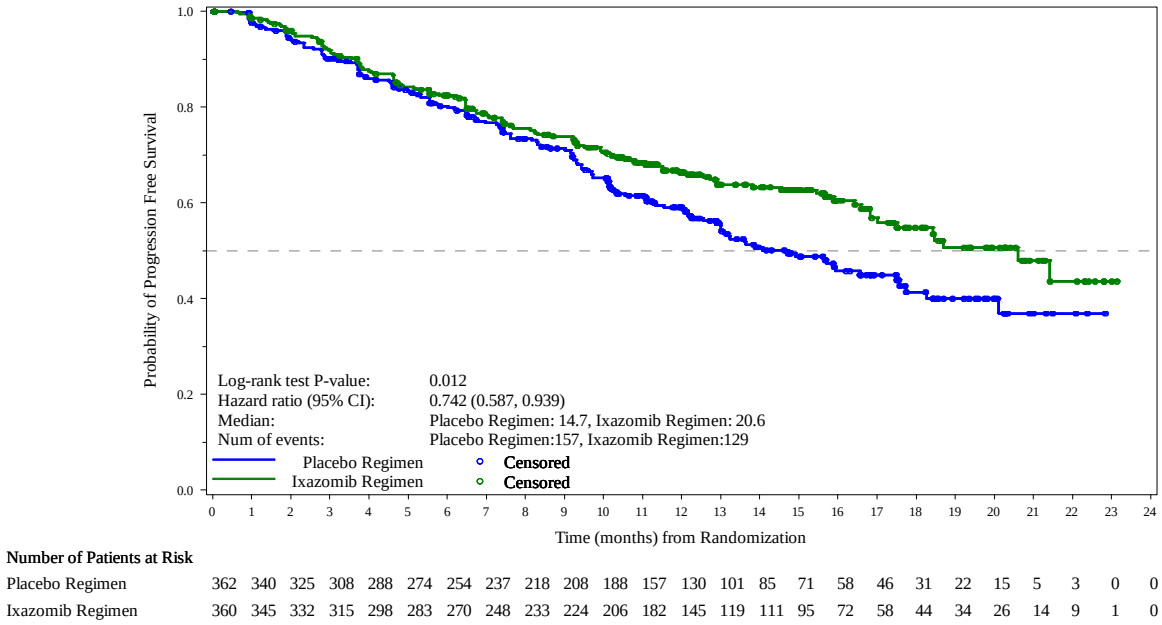
Table 6 Progression Free Survival Results in Multiple Myeloma Patients Treated with NINLARO or Placebo in Combination with Lenalidomide and Dexamethasone (Intent-to-Treat Population)

	NINLARO + Lenalidomide and Dexamethasone (N = 360)	Placebo + Lenalidomide and Dexamethasone (N = 362)
Progression-free Survival		
Events, n (%)	129 (36)	157 (43)
Median (months)	20.6	14.7
Hazard Ratio* (95% CI)	0.74 (0.587, 0.939)	
p-value†	0.012	
Response rate		
Overall Response Rate‡, n (%)	282 (78.3)	259 (71.5)
Complete Response	42 (11.7)	24 (6.6)
Very Good Partial Response	131 (36.4)	117 (32.3)
Partial Response	109 (30.3)	118 (32.6)
Time to Response, months		
Median	1.1	1.9
Duration of Response§, months		
Median	20.5	15.0

*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.
† P-value is based on the stratified log-rank test.
‡ORR = CR+PR+VGPR
§Based on responders in the response-evaluable population

The NINLARO regimen demonstrated a statistically significant improvement in the median PFS compared to the placebo regimen as seen below in Figure 1.

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

At the time of the first pre-specified analysis, median overall survival had not been reached in either regimen of the intent-to-treat (ITT) population at a median follow up of 14.7 months. One hundred seven patients had died and more deaths occurred in patients receiving the placebo regimen (15.5%) compared to patients receiving the NINLARO regimen (14.2%). Overall survival in the subset of high risk patients whose multiple myeloma harbours deletion of chromosome 17 (del[17]) was also a pre-specified endpoint and was assessed centrally at a CLIA-certified laboratory. More deaths occurred in patients with del(17) receiving the placebo regimen (27.3%) compared with patients receiving the NINLARO regimen (11.1%).

Patients with high risk cytogenetic abnormalities whose myeloma harbours del(17), translocation of chromosomes 4 and 14 (t[4:14]), translocation of chromosomes 14 and 16 (t[14:16]) or a combination of the three abnormalities were enrolled in the Phase 3 study. The results of the pre-specified prospective analyses demonstrated median PFS with the NINLARO regimen were similar in patients with and without del(17). Median PFS in patients with del(17) and the overall high-risk population was 21.4 months in the NINLARO regimen compared to 9.7 months in the placebo regimen.

Quality of life as assessed by global health scores (EORTC QLQ-C30 and MY-20) was maintained during treatment and was similar in both treatment regimens.

A planned interim analysis for overall survival (OS) at a median follow up of 23 months was conducted with 35% of the required number of deaths for final OS analysis in the ITT population; there were 81 deaths in the NINLARO regimen and 90 deaths in the placebo regimen. Median overall survival was not reached in either regimen. At the same time, a non-inferential exploratory PFS analysis was conducted. Estimated median PFS was 20 months in the NINLARO regimen and 15.9 months in the placebo regimen (HR=0.82, 95% CI [0.67, 1.0]) in the ITT population.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After oral administration, peak plasma concentrations of ixazomib were achieved at approximately one hour after dosing. The mean absolute oral bioavailability is 58% (Relative Standard Error = 9%) based on the population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2-10.6 mg.

Administration with a high-fat meal decreased ixazomib AUC by 28% and C_{max} by 69% compared with administration after an overnight fast (see 4.2 Dose and Method of Administration).

Distribution

Ixazomib is 99% bound to plasma proteins and distributes into red blood cells with a blood to plasma AUC ratio of 10. The steady-state volume of distribution is 543 L based on the population PK analysis.

Metabolism

After oral administration of a radiolabeled dose, 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

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 (t1/2) of ixazomib was 9.5 days. Approximately 2-fold accumulation in AUC was observed with weekly oral dosing on Day 15.

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 faeces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

Special Populations

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=13) or severe hepatic impairment at 1.5 mg (total bilirubin > 3 x ULN, N=18). Unbound dose normalized AUC was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function (see 4.2 Dose and Method of Administration).

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=18), severe renal impairment (creatinine clearance < 30 mL/min, N=14), or ESRD requiring dialysis (N=6). Unbound AUC was 38% higher in patients with severe renal impairment or ESRD requiring dialysis as compared to patients with normal renal function. Pre- and post-dialyser concentrations of ixazomib measured during the haemodialysis session were similar, suggesting that ixazomib is not dialysable (see 4.2 Dose and Method of Administration).

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 in an *in vivo* comet assay in mice, in which percent tail DNA was assessed in the stomach and liver. Therefore, the weight of evidence supports that NINLARO is not considered to present a genotoxic risk.

Carcinogenicity

No carcinogenicity studies have been performed with ixazomib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients include microcrystalline cellulose, magnesium stearate and purified talc. All capsule shells contain gelatin and titanium dioxide. The 4 mg capsule shell contains iron oxide red and iron oxide yellow, the 3 mg capsule shell contains iron oxide black and the 2.3 mg capsule shell contains iron oxide red. The capsules are imprinted with TekPrint SW-9008 Black Ink (ARTG PI No 2328).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

Refer to Section 4.5 for Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C. Do not freeze. Store capsules in the original packaging until just prior to dosing.

6.5 NATURE AND CONTENTS OF CONTAINER

NINLARO is available in two pack sizes:

- 1 capsule or

- 3 capsules (multi-pack with three one capsule cartons)

Not all pack sizes may be marketed.

Capsules are individually packaged in a PVC-Aluminium/Aluminium blister.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ixazomib is a Class 3 compound, as per the Biopharmaceutics Classification System (BCS). 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. The calculated aLogP for Ixazomib citrate at 25°C gives a theoretical value of 3.50. The polymorphic Form 2 is used in the manufacture of NINLARO.

Ixazomib citrate has one chiral centre and has been unambiguously determined to be the R stereoisomer. *In vivo* conversion to the S-stereoisomer does not occur after administration.

Chemical structure

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

Molecular formula: $C_{20}H_{23}BCl_2N_2O_9$

Molecular weight: 517.12

CAS number

1239908-20-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney, NSW 2000
Australia

Tel: 1800 675 957

www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

15 November 2016

10 DATE OF REVISION

24 February 2021

Summary table of changes

Section changed	Summary of new information
All	Minor editorial changes
4.8	Addition of Post-Marketing information
4.9	Addition of information on overdose
8	Update of Sponsor's address