NINLARO Approved PACKAGE INSERT

PROFESSIONAL INFORMATION

SCHEDULING STATUS

4

1. NAME OF THE MEDICINE

NINLARO 2,3 mg hard capsules

NINLARO 3 mg hard capsules

NINLARO 4 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NINLARO 2.3 mg hard capsules

Each light pink capsule contains 2,3 mg of ixazomib (as 3,3 mg of ixazomib citrate)

NINLARO 3 mg hard capsules

Each light grey capsule contains 3 mg of ixazomib (as 4,3 mg of ixazomib citrate)

NINLARO 4 mg hard capsules

Each light orange capsule contains 4 mg of ixazomib (as 5,7 mg of ixazomib citrate)

For the full list of excipients, (see 6.1 *List of excipients)*

3. PHARMACEUTICAL FORM

Hard capsule.

NINLARO 2.3 mg hard capsules

Light pink, size 4 gelatin hard capsule, marked “Takeda” on the cap and “2.3 mg” on the body with black ink.

NINLARO 3 mg hard capsules

Light grey, size 4 gelatin hard capsule, marked “Takeda” on the cap and “3 mg” on the body with black ink.

NINLARO 4 mg hard capsules

Light orange, size 3 gelatin hard capsule, marked “Takeda” on the cap and “4 mg” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with recurrent or relapsed multiple myeloma who have received at least one prior therapy.

4.2 Posology and method of administration

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

Posology

The recommended starting dose of ixazomib is 4 mg 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.

Dosing Schedule: NINLARO taken with lenalidomide and dexamethasone

28-Day Cycle (a 4-week cycle)								
	Week 1		**Week 2**		**Week 3**		**Week 4**	
	Day 1	Days 2 to 7	Day 8	Days 9 to 14	Day 15	Days 16 to 21	Day 22	Days 23 to 28
NINLARO	✔		✔		✔			
Lenalidomide	✔	✔ Daily	✔	✔ Daily	✔	✔ Daily		
Dexamethasone	✔		✔		✔		✔	

✔ intake of medicinal product

For additional information regarding lenalidomide and dexamethasone, refer to the professional information for these medical products.

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-haematologic toxicities should, at the medical practitioner's discretion, generally have reversed to patient's baseline condition or ≤ Grade 1

Treatment should be continued until disease progression or unacceptable toxicity. Treatment with ixazomib in combination with lenalidomide and dexamethasone for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited (see 5.1 *Pharmacodynamic properties*).

Delayed or missed doses

In the event that an ixazomib 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.

Dose modifications

The NINLARO dose reduction steps are provided in Table 1 and the dose modification guidelines are provided in Table 2.

Table 1: NINLARO dose reduction steps

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 thrombocytopaenia, neutropenia and rash. For these toxicities, the first dose modification step is to withhold/reduce lenalidomide. Refer to the lenalidomide professional information for the dose reduction steps for these toxicities.

Table 2: Dose modifications guidelines for NINLARO in combination with lenalidomide and dexamethasone

Haematological toxicities	**Recommended actions**
Thrombocytopenia (platelet count)	
Platelet count < 30 000/mm^3	• Withhold NINLARO and lenalidomide until platelet count ≥ 30 000/mm^3. • Following reversal, resume lenalidomide at the next lower dose according to its professional information and resume NINLARO at its most recent dose. • If platelet count falls to < 30 000/mm^3 again, withhold NINLARO and lenalidomide until platelet count ≥ 30 000/mm^3. • Following reversal, resume NINLARO at the next lower dose and resume lenalidomide at its most recent dose*
Neutropenia (absolute neutrophil count)	
Absolute neutrophil count < 500/mm^3	• Withhold NINLARO and lenalidomide until platelet count ≥ 500/mm^3. Consider adding G-CSF (Growth Factor Support) as per clinical guidelines.

	• Following reversal, resume lenalidomide at the next lower dose according to its professional information and resume NINLARO at its most recent dose. • If absolute neutrophil count falls to < 500/mm^3 again, withhold NINLARO and lenalidomide until platelet count ≥ 500/mm^3. • Following reversal, 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 reversal, resume lenalidomide at the next lower dose according to its professional information. • If Grade 2 or 3 rash occurs again, withhold NINLARO and lenalidomide until rash recovers to ≤ Grade 1. • Following reversal, 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 reversal, resume NINLARO at its most recent dose.

Grade 2 peripheral neuropathy with Pain or Grade 3 peripheral neuropathy	• Withhold NINLARO. Toxicities should, at the medical practitioner's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming NINLARO. • Following reversal, 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 medical practitioner'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 reversal.

*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 NINLARO 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.

Thromboprophylaxis is recommended in patients being treated with NINLARO in combination with lenalidomide and dexamethasone and should be based on an assessment of the patient's underlying risks and clinical status.
For other concomitant medicinal products that may be required, refer to the current lenalidomide and dexamethasone professional information.

Special Patient Populations

Elderly

No dose adjustment of NINLARO is required for patients over 65 years of age.
Discontinuations in patients > 75 years of age were reported in 13 patients (28 %) in the NINLARO regimen and 10 patients (16 %) in the placebo regimen. Cardiac dysrhythmias in patients > 75 years of age were observed in 10 patients (21 %) in the NINLARO regimen and 9 patients (15 %) in the placebo regimen.

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). The reduced 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. (see section 5.2 *Pharmacokinetic properties*).

Renal impairment
No dose adjustment of NINLARO is required for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min). The reduced 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. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis (see section 5.2 *Pharmacokinetic properties*).
Refer to the lenalidomide professional information for dosing recommendations in patients with renal impairment.
Paediatric population
The safety and efficacy of NINLARO in children below 18 years of age have not been established. No data are available.

Method of administration
NINLARO is for oral use.
The absorption of NINLARO is decreased after a fatty meal. NINLARO should be taken at approximately the same time on days 1, 8, and 15 of each treatment cycle at least 1 hour before or at least 2 hours after food (see section 5.2 *Pharmacokinetic properties*). The capsule should be swallowed whole with water. It should not be crushed, chewed, or opened (see section 6.6 *Special precautions for disposal and other handlin*g).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (*List of excipients*).

As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the professional information for these medicinal products for additional contraindications.
Pregnancy and lactation

4.4 Special warnings and precautions for use
As NINLARO is administered in combination with lenalidomide and dexamethasone,

Thrombocytopaenia
Thrombocytopaenia has been reported with NINLARO (see section 4.8 *Undesirable effects*) with platelet nadirs typically occurring between Days 14 - 21 of each 28 -day cycle and reverse to baseline by the start of the next cycle (see section 4.8 *Undesirable effects*).

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 professional information. Thrombocytopaenia can be managed with dose modifications (see section 4.2 *Posology and method of administration*) and platelet transfusions as per standard medical guidelines.

Gastrointestinal toxicities
Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, that may require use of antiemetic and anti-diarrhoeal medicinal products and supportive care (see section 4.8 *Undesirable effects*). The dose should be adjusted downwards for severe (Grade 3 - 4) symptoms (see 4.2 *Posology and method of administration*). In case of severe gastrointestinal events, monitoring of serum potassium level is recommended and dose reduction or discontinuation of treatment may be necessary.

Peripheral neuropathy
Peripheral neuropathy has been reported with NINLARO (see section 4.8 *Undesirable effects*). The patient should be monitored for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification (see section 4.2 *Posology and method of administration*).

Peripheral oedema

Peripheral oedema has been reported with NINLARO (see section 4.8 *Undesirable effects*). The patient should be evaluated for underlying causes and provide supportive care, as necessary. The dose of dexamethasone should be adjusted per its prescribing information or ixazomib for Grade 3 or 4 symptoms (see section 4.2 *Posology and method of administration*).

Cutaneous reactions

Rash has been reported with NINLARO (see section 4.8 *Undesirable effects*). Rash should be managed with supportive care or with dose modification if Grade 2 or higher (see 4.2 *Posology and method of administration*). Severe cutaneous adverse reactions (SCARs) including Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) which can be life-threatening or fatal have also been rarely reported in association with ixazomib treatment (see section 4.8 *Undesirable effects*).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, ixazomib should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS or TEN with the use of ixazomib, treatment with ixazomib must not be restarted in this patient at any time.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP), have been reported in patients who received ixazomib. Some of these events have been fatal. Signs and symptoms of TMA should be monitored for. If the diagnosis is suspected, stop ixazomib and evaluate patients for possible TMA. If the diagnosis of TMA is excluded, ixazomib can be restarted. The safety of reinitiating ixazomib therapy in patients previously experiencing TMA is not known.

Hepatotoxicity

Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have been uncommonly reported with NINLARO (see section 4.8 *Undesirable effects*). Hepatic enzymes should be monitored regularly and the dose should be adjusted for Grade 3 or 4 symptoms (see section 4.2 *Posology and method of administration).*

Pregnancy

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 foetus. (See section section 4.3).

Women of childbearing potential must use highly effective contraception while taking NINLARO and for 90 days after stopping treatment (*see* section *4.5 Interactions with other medicinal products and 4.6 Fertility, pregnancy and lactation*). Women using hormonal contraceptives should additionally use a barrier method of contraception**.**

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) has occurred in patients receiving NINLARO. PRES is a rare, reversible, neurological disorder which can present with seizures, hypertension, headache, altered consciousness, and visual disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. In patients developing PRES, discontinue NINLARO.

Strong CYP3A inducers

Strong inducers may reduce the efficacy of NINLARO therefore the concomitant use of strong CYP3A inducers such as carbamazepine, phenytoin, rifampicin and St. John's Wort (*Hypericum perforatum*), should be avoided (*see section 4.5 Interactions with other medicinal products and section 5.2 Pre-clinical safety data*). Closely monitor patients for disease control if co-administration with a strong CYP3A inducer cannot be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

CYP inhibitors

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

Co-administration of NINLARO with strong CYP1A2 inhibitors did not result in a clinically meaningful change in the systemic exposure of NINLARO based on the results of a population pharmacokinetic (PK) analysis. Therefore, no dose modification is required for NINLARO with co-administration of strong CYP1A2 inhibitors.

CYP inducers

Co-administration of NINLARO with rifampicin decreased ixazomib C_{max} by 54 % and AUC by 74 %. Therefore, co-administration of strong CYP3A inducers with NINLARO is not recommended (*see 4.4 Special warnings and precautions for use).*

Effect of ixazomib on other medicinal products

NINLARO is not a reversible or a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. NINLARO 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

NINLARO is a low affinity substrate of P-gp. NINLARO is not a substrate of BCRP, MRP2 or hepatic OATPs. NINLARO 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.

Oral contraceptives

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 hormonal contraceptives should additionally use a barrier method of contraception.

4.6 Fertility, pregnancy and lactation

NINLARO use is contraindicated in pregnancy (See section 4.3)

Women of childbearing potential/Contraception in males and females

Male and female patients who are able to have children must use effective contraceptive measures during and for 90 days following treatment. NINLARO is contraindicated in women of childbearing potential not using contraception.

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. Therefore, women using oral hormonal contraceptives should additionally use a barrier method of contraception.

Pregnancy

NINLARO is contraindicated during pregnancy as it can cause foetal harm when administered to a pregnant woman. Therefore, women should avoid becoming pregnant while being treated with NINLARO.

Studies in animals have shown reproductive toxicity (*see section 5.3 Preclinical safety data*).

NINLARO is given in combination with lenalidomide. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect in humans is expected. The conditions of the Pregnancy Prevention Programme for lenalidomide must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential. Please refer to the current lenalidomide professional information.

Breast-feeding

Mothers taking NINLARO must not breastfeed their infants. See section 4.3

Fertility

Fertility studies have not been conducted with NINLARO (*see section 5.3 Preclinical safety data*).

4.7 Effects on ability to drive and use machines

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 Undesirable effects

As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the professional information for these medicinal products for additional undesirable effects.

Summary of the safety profile

The data presented below is the pooled safety data from the pivotal, Phase 3, global C16010 study (n = 720) and the double-blind, placebo-controlled C16010 China Continuation Study (n = 115). The most frequently reported adverse reactions (≥ 20 %) across 418 patients treated within the ixazomib regimen and 417 patients within the placebo regimen were diarrhoea (47 % vs. 38 %), thrombocytopaenia (41 % vs. 24 %), neutropenia (37 % vs. 36 %), constipation (31 % vs. 24 %), upper respiratory tract infection (28 % vs. 24 %), peripheral neuropathy (28 % vs. 22 %), nausea (28 % vs. 20 %), back pain (25 % vs. 21 %), rash (25 % vs. 15 %), peripheral oedema (24 % vs. 19 %), vomiting (23 % vs. 12 %) and bronchitis (20 % vs. 15 %). Serious adverse reactions reported in ≥ 2 % of patients included diarrhoea (3 %) thrombocytopaenia (2 %) and bronchitis (2 %).

Tabulated list of adverse reactions

The following convention is used for the classification of the frequency of an adverse drug reaction (ADR): very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with NINLARO in combination with lenalidomide and dexamethasone (all Grades, grade 3 and grade 4)

System Organ Class/Adverse reaction	**Adverse Reactions (All Grades)**	**Grade 3 Adverse Reactions**	**Grade 4 Adverse Reactions**
Infections and infestations			
Upper respiratory tract infection	Very Common	Common	
Bronchitis	Very Common	Common	

Herpes zoster	Common	Common	
Blood and lymphatic system disorders			
Thrombocytopaenia*	Very Common	Very Common	Common
Neutropaenia*	Very Common	Very Common	Common
Thrombotic microangiopathy	Rare		Rare
Thrombotic thrombocytopenic purpura†	Rare	Rare	Rare
Immune system disorders			
Anaphylactic reaction†	Rare	Very rare	Very rare
Angioedema†	Rare	Rare	
Metabolism and nutrition disorders			
Tumour lysis syndrome†	Rare	Rare	Rare
Nervous system disorders			
Peripheral neuropathies*	Very Common	Common	
Posterior reversible encephalopathy disorders*†	Rare	Rare	Rare
Transverse myelitis†	Rare	Rare	
Gastro-intestinal disorders			
Diarrhoea	Very Common	Common	
Constipation	Very Common	Uncommon	
Nausea	Very Common	Common	
Vomiting	Very Common	Uncommon	
Skin and subcutaneous tissue disorders			
Rash*	Very Common	Common	
Stevens-Johnson syndrome†	Rare	Rare	
Acute febrile neutrophilic dermatosis	Rare	Rare	
Toxic epidermal necrolysis†	Rare		Rare

Musculoskeletal and connective tissue disorders			
Back pain	Very Common	Uncommon	
Arthralgia	Very common	Common	
General disorders and administration site conditions			
Oedema peripheral	Very Common	Common	
Pyrexia	Very common	Uncommon	

Note: ADRs included as preferred terms are based on MedDRA version 23.0.

*Represents a pooling of preferred terms.

†Reported outside of the Phase 3 studies

Description of selected adverse reactions

Discontinuations

For each adverse reaction, one or more of the three medicinal products was discontinued in ≤ 1 % of patients in the ixazomib regimen.

Thrombocytopaenia

Two percent of patients in both the ixazomib regimen and in the placebo regimen had a platelet count ≤ 10 000/mm^3 during treatment. Less than 1 % of patients in both regimens had a platelet count ≤ 5 000/mm^3 during treatment. Thrombocytopaenia resulted in discontinuation of one or more of the three medicinal products in <2 % of patients in the ixazomib regimen and 3 % of patients in the placebo regimen. Thrombocytopaenia did not result in an increase in haemorrhagic events or platelet transfusions.

Gastrointestinal toxicities

Diarrhoea resulted in discontinuation of one or more of the three medicinal products in 2 % of patients in the ixazomib regimen and 1 % of patients in the placebo regimen.

Rash

Rash occurred in 25 % of patients in the ixazomib regimen compared to 15 % of patients in the placebo regimen. The most common type of rash reported in both regimens was maculo-papular and macular rash. Grade 3 rash was reported in 3 % of patients in the ixazomib regimen compared to 2 % of patients in the placebo regimen. Rash resulted in discontinuation of one or more of the three medicinal products in < 1 % of patients in both regimens.

Peripheral neuropathy

Peripheral neuropathy occurred in 28 % of patients in the ixazomib regimen compared to 22 % of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported in 2 % of patients in the ixazomib regimen compared to 1 % in the placebo regimen. The most commonly reported reaction was peripheral sensory neuropathy (21 % and 15 % in the ixazomib and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<3 %). Peripheral neuropathy resulted in discontinuation of one or more of the three medicinal products in 3 % of patients in the ixazomib regimen compared to <1 % of patients in the placebo regimen.

Eye disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 34 % in patients in the ixazomib regimen and 28 % of patients in the placebo regimen. The most common adverse reactions were blurred vision (6 % in the ixazomib regimen and 5 % in the placebo regimen), dry eye (6 % in the ixazomib regimen and 1 % in the placebo regimen), conjunctivitis (8 % in the ixazomib regimen and 2 % in the placebo regimen) and cataract (13 % in the ixazomib regimen and 17 % in the placebo regimen). Grade 3 adverse reactions were reported in 6 % of patients the ixazomib regimen and 8 % of patients in the placebo regimen.

Other adverse reactions

In the pooled dataset from the pivotal, Phase 3, global C16010 study (n=720) and the double-blind, placebo-controlled, C16010 China Continuation Study (n=115), the following adverse reactions occurred with a similar rate between the ixazomib and placebo regimens: fatigue (28 % vs. 26 %), decreased appetite (13 % vs. 11 %), hypotension (5 % vs. 4 %), heart failure† (5 % each), arrhythmia† (17 % vs. 16 %), and liver impairment including enzyme changes† (11 % vs. 9 %).

The frequency of severe (Grade 3 - 4) events of hypokalaemia was higher in the ixazomib regimen (5 %) than the placebo regimen (<2 %).

Fungal and viral pneumonia resulting in fatal outcome were rarely reported (less than 1 %) in patients given the ixazomib, lenalidomide and dexamethasone combination.

†Standardised MedDRA Queries (SMQs)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com

4.9 Overdose

Overdose has been reported in patients taking NINLARO. Symptoms of overdose are generally consistent with the known risks of NINLARO (see section 4.8). Overdose of 12 mg (taken at one time) has resulted in serious adverse events, such as severe nausea, aspiration pneumonia, multiple organ failure and death.

There is no known specific antidote for ixazomib overdose. In the event of an overdose, monitor the patient closely for adverse reactions (see section *4.8 Undesirable effects*) and provide appropriate supportive care. Ixazomib is not dialyzable (see section 5.2).

Overdoses were most common in patients starting treatment with NINLARO. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Instruct patients to take the recommended dosage as directed because overdose has led to deaths.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological group: Antineoplastic agents, other antineoplastic, ATC code: L01XG03

Mechanism of action

Ixazomib citrate, a prodrug, is a substance that rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib. Ixazomib is an oral, highly 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. *In vitro*, ixazomib affected cell types found in the bone marrow microenvironment including vascular endothelial cells, osteoclasts and osteoblasts.

Cardiac electrophysiology

Ixazomib did 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 was estimated to be 0.07 msec (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 ixazomib on heart rate.

Clinical efficacy and safety

The efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone was evaluated in an international randomised, double-blind, placebo-controlled, multicenter Phase 3 superiority study (C16010) in patients with relapsed and/or refractory multiple myeloma who had received at least one prior therapy. A total of 722 patients (intent-to-treat [ITT] population) were randomised in a 1:1 ratio to receive either the combination of ixazomib, lenalidomide, and dexamethasone (N=360; ixazomib regimen) or placebo, lenalidomide and dexamethasone (N=362; placebo regimen) until disease progression or unacceptable toxicity. Patients enrolled in the trial had multiple myeloma that was refractory, including primary refractory, had relapsed after prior therapy, or had relapsed and was refractory to any prior therapy. Patients that changed therapies prior to disease progression were eligible for enrolment, as well as those with controlled cardiovascular conditions. The Phase 3 study excluded patients who were refractory to lenalidomide or proteasome inhibitors and patients who received more than three prior therapies. 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. As data are limited in these patients, a careful risk-benefit assessment is recommended before initiating the ixazomib regimen.

Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide professional information. Concomitant medicinal products, such as antiemetic, antiviral, and antihistamine medicinal products were given to patients at the doctor's discretion as prophylaxis and/or management of symptoms.

Patients received ixazomib 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 professional information. Treatment continued until disease progression or unacceptable toxicities.

The baseline demographics and disease characteristics were balanced and comparable between the study regimens. The median age was 66 years, range 38 -91 years; 58 % of patients were older than 65 years. Fifty seven percent of patients were male. Eighty five percent of the population was White, 9 % Asian and 2 % Black. Ninety three percent of patients had an ECOG performance status of 0 -1 and 12 % had baseline ISS stage III disease (N=90). Twenty five percent of patients had a creatinine clearance of < 60 mL/min. Twenty three percent of patients had light chain disease and 12 % of patients had measurable disease by free light chain assay only. Nineteen percent had high-risk cytogenetic abnormalities (del[17], t[4;14], t[14;16]) (N=137), 10 % had del(17) (N=69) and 34 % had 1q amplification (1q21) (N=247). Patients received one to three prior therapies (median of 1) including prior treatment with bortezomib (69 %), carfilzomib (<1 %), thalidomide (45 %), lenalidomide (12 %), melphalan (81 %). Fifty seven percent of patients had undergone prior stem cell transplantation. Seventy seven percent of patients relapsed after prior therapies and 11 % were refractory to prior therapies. Primary refractory, defined as best response of stable disease or disease progression on all prior therapies, was documented in 6 % of patients.

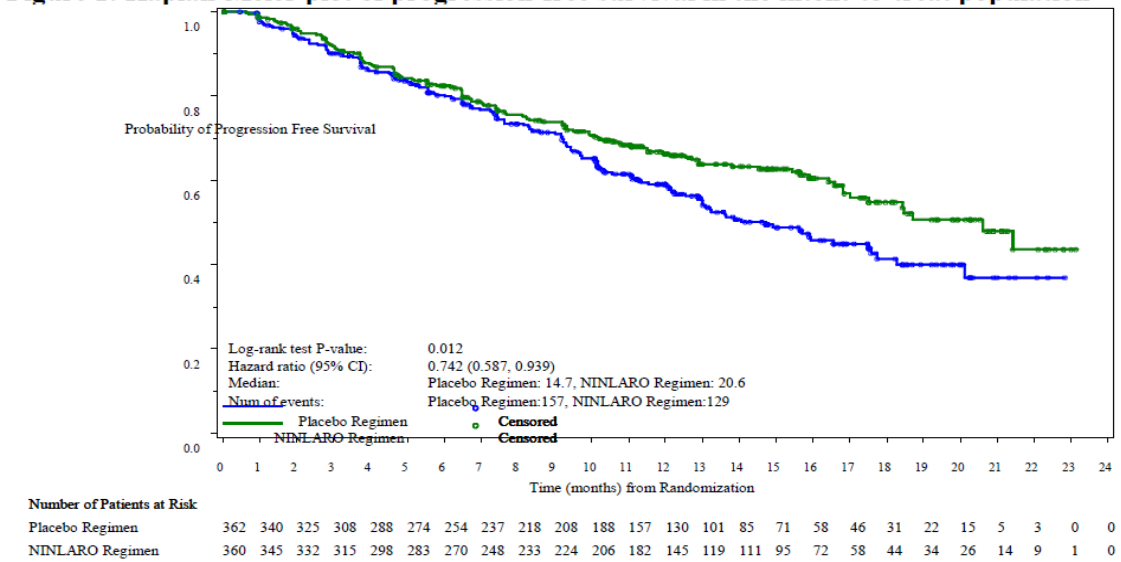
The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central laboratory results. Response was assessed every 4 weeks until disease progression. At the primary analysis (median follow up of 14.7 months and a median of 13 cycles), PFS was statistically significantly different between the treatment arms. PFS results are summarised in Table 4 and Figure 1. The improvement in PFS in the ixazomib regimen was supported by improvements in overall response rate.

Table 4: Progression free survival and response Results in multiple myeloma patients treated with ixazomib or placebo in combination with lenalidomide and dexamethasone (intent-to-treat population)

	Ixazomib +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
p-value*	0,012	
Hazard Ratio[+] (95 % CI)	0,74 (0,59; 0,94)	
Overall Response Rate[ǂ], n (%)	282 (78,3)	259 (71,5)
Response Category, n (%)		
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

* P-value is based on the stratified log-rank test.
[+] Hazard Ratio is based on a stratified Cox's proportional hazard regression model. A hazard ratio less than 1 indicates an advantage for the ixazomib regimen.
[ǂ] ORR = CR+VGPR+PR
[§] Based on responders in the response-evaluable population.

Figure 1: Kaplan-Meier plot of progression-free survival in the intent-to-treat population



A second, non-inferential, PFS analysis was conducted with a median follow up of 23 months. At this analysis, estimated median PFS was 20 months in the ixazomib regimen and 15,9 months in the placebo regimen (HR=0,82 [95 % CI (0,67; 1,0)]) in the ITT population. For patients with one prior therapy, the median PFS was 18,7 months in the ixazomib regimen and 17,6 months in the placebo regimen (HR=0,99). For patients with 2 or 3 prior therapies PFS was 22,0 months in the ixazomib regimen and 13,0 months in the placebo regimen (HR=0,62). At the final analysis for OS at a median duration of follow up of approximately 85 months, median OS in the ITT population was 53,6 months for patients in the ixazomib regimen and 51,6 months for patients in the placebo regimen (HR = 0,94 [95 % CI: 0,78; 1,13; p = 0,495]). For patients with one prior therapy, the median OS was 54,3 months in the ixazomib regimen and 58,3 months in the placebo regimen (HR = 1,02 [95 % CI: 0,80; 1,29]). For patients with 2 or 3 prior therapies, the median OS was 53,0 months in the ixazomib regimen and 43,0 months in the placebo regimen (HR = 0,85 [95 % CI: 0,64; 1,11]).

A randomised, double-blind, placebo-controlled Phase 3 study was conducted in China (N=115) with a similar study design and eligibility criteria. Many of the patients enrolled in the study had advanced disease with Durie-Salmon Stage III (69 %) at initial diagnosis and a treatment history of receiving at least

2 prior therapies (60 %) and being thalidomide refractory (63 %). At the primary analysis (median follow up of 8 months and a median of 6 cycles), the median PFS was 6,7 months in the ixazomib regimen compared to 4 months in the placebo regimen (p-value=0,035, HR=0,60). At the final analysis for OS at a median follow up of 19.8 months, OS was improved for patients treated in the ixazomib regimen compared with placebo [p-value=0.0014, HR=0,42, 95 % CI: 0,242; 0,726]). As multiple myeloma is a heterogeneous disease, benefit may vary across subgroups in the Phase 3 study (C16010).

In the Phase 3 study (C16010), 10 patients (5 in each treatment regimen) had severe renal impairment at baseline. Of the 5 patients in the ixazomib regimen, one patient had a confirmed partial response and 3 confirmed stable disease (however 2 were unconfirmed partial response and 1 was an unconfirmed very good partial response). Of the 5 patients in the placebo regimen, 2 had a confirmed very good partial response.

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 in the Phase 3 study (C16010).

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 %. 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 % compared with administration after an overnight fast (see section *4.2 Posology 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.

Biotransformation

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 %).

Elimination

Ixazomib exhibits a multi-exponential disposition profile. Based on a population PK analysis, systemic clearance (CL) was approximately 1,86 L/hr 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.

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 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 section *4.2 Posology 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-dialyzer

concentrations of ixazomib measured during the haemodialysis session were similar, suggesting that ixazomib is not dialyzable (see section *4.2 Posology 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. The mean AUC was 35 % higher in Asian patients; however, there was overlap in the AUC of ixazomib across White and Asian patients.

5.3 Preclinical safety data

Mutagenicity

Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay) or clastogenic in a bone marrow micronucleus assay in mice. Ixazomib was 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 indicates that ixazomib is not considered to present a genotoxic risk.

Reproductive and embryo-foetal development

Ixazomib caused embryo-foetal toxicity in pregnant rats and rabbits only at maternally toxic doses and at exposures that were slightly higher than those observed in patients receiving the recommended dose. Studies of fertility and early embryonic development and pre- and post-natal 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 and/or pharmacology

In multi-cycle repeated-dose toxicity studies conducted in rats and dogs, the principal target organs included the gastrointestinal tract, lymphoid tissues, and the nervous system. In the 9-month study (10 cycles) in dogs orally administered with a dosing schedule mimicking the clinical regimen (28-day cycle), microscopic neuronal effects were generally minimal in nature and only observed at 0,2mg/kg (4 mg/m^2). The majority of target organ findings demonstrated partial to full reverse following discontinuation of treatment, with the exception of neuronal findings in the lumbar dorsal root ganglion and dorsal column.

Following oral administration, a tissue distribution study in rats revealed that the brain and spinal cord were amongst the tissues with the lowest levels, suggesting that the penetration of ixazomib through the blood-brain barrier appears to be limited. However, the relevance to humans is unknown. Non-clinical safety pharmacology studies both *in vitro* (on hERG channels) and *in vivo* (in telemetered dogs following single oral administration) demonstrated no effects of ixazomib on cardiovascular or respiratory functions at AUC more than 8-fold higher than the clinical value.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NINLARO 2,3 mg hard capsules

Capsule contents

Microcrystalline cellulose

Magnesium stearate

Talc

Capsule shell

Gelatin

Titanium dioxide (E171)

Red iron oxide (E172)

Printing ink

Shellac

Propylene glycol

Potassium hydroxide

Black iron oxide (E172)

NINLARO 3 mg hard capsules

Capsule contents

Microcrystalline cellulose
Magnesium stearate
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Black iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

NINLARO 4 mg hard capsules
Capsule contents
Microcrystalline cellulose
Magnesium stearate
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink

Shellac

Propylene glycol

Potassium hydroxide

Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30° C. Do not freeze.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC-Aluminium /Aluminium blister sealed inside a wallet pack containing one capsule.

Three single blister wallet packs are packaged in one carton.

6.6 Special precautions for disposal and other handling

Ixazomib is cytotoxic. The capsule should not be removed until just prior to dosing. The capsules should not be opened or crushed. Direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid raising dust during clean-up. If contact occurs, wash thoroughly with soap and water.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd
Building A, Monte Circle
64 Montecasino Boulevard
Fourways
2191
Tel: +27 11 514 3000

8. MARKETING AUTHORISATION NUMBER(S)

Ninlaro 2,3 mg: 51/26/0956
Ninlaro 3 mg: 51/26/0957
Ninlaro 4mg: 51/26/0958

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2nd February 2021

10. DATE OF REVISION OF THE TEXT

4 March 2025