NINLARO®

1. NAME OF THE MEDICINAL PRODUCT

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 capsule contains 2.3 mg of ixazomib (as 3.3 mg of ixazomib citrate)

NINLARO 3 mg hard capsules
Each capsule contains 3 mg of ixazomib (as 4.3 mg of ixazomib citrate)

NINLARO 4 mg hard capsules
Each capsule contains 4 mg of ixazomib (as 5.7 mg of ixazomib citrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

NINLARO 2.3 mg hard capsules
Light pink, size 4 hard gelatin 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 hard gelatin capsule, marked "Takeda" on the cap and "3 mg" on the body with black ink.

NINLARO 4 mg hard capsules
Light orange, size 3 hard gelatin 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 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 physician experienced in the management of multiple myeloma.

Posology

The recommended starting dose of NINLARO 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 Summary of Product Characteristics (SmPC) for these medicinal products.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be ≥ 1,000/mm3
- Platelet count should be ≥ 75,000/mm3
- 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. Treatment with NINLARO 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 section 5.1).

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 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 presented 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	

*Recommended reduced dose of 3 mg in the presence of 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, neutropenia and rash. For these toxicities, the first dose modification step is to withhold/reduce lenalidomide. Refer to the lenalidomide SmPC, section 4.2 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/mm3. • Following recovery, resume lenalidomide at the next lower dose according to its SmPC and resume NINLARO at its most recent dose. • If platelet count falls to < 30,000/mm3 again, withhold NINLARO and lenalidomide until platelet count ≥ 30,000/mm3. • Following recovery, 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 absolute neutrophil count is ≥ 500/mm3. 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 < 500/mm3 again, withhold NINLARO and lenalidomide until absolute neutrophil count is ≥ 500/mm3. • 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 SmPC. • 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 Grade 3 or 4 non-hematological toxicities	• Withhold NINLARO. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming NINLARO. • If attributable to NINLARO, resume NINLARO 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 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 SmPC.

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 arrhythmias 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 in patients with moderate (total bilirubin > 1.5-3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment (see section 5.2).

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 in 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).

Refer to the lenalidomide SmPC 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.
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). The capsule should be swallowed whole with water. It should not be crushed, chewed, or opened (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the SmPC for these medicinal products for additional special warnings and precautions for use.

Thrombocytopenia

Thrombocytopenia has been reported with NINLARO (see section 4.8) 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 section 4.8).

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 SmPC. Thrombocytopenia can be managed with dose modifications (see section 4.2) and platelet transfusions as per standard medical guidelines.

Gastrointestinal toxicities

Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care (see section 4.8). The dose should be adjusted for severe (Grade 3-4) symptoms (see section 4.2). In case of severe gastrointestinal events, monitoring of serum potassium level is recommended.

Peripheral neuropathy
Peripheral neuropathy has been reported with NINLARO (see section 4.8). 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).

Peripheral oedema

Peripheral oedema has been reported with NINLARO (see section 4.8). 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 NINLARO for Grade 3 or 4 symptoms (see section 4.2).

Cutaneous reactions

Rash has been reported with NINLARO (see section 4.8). Rash should be managed with supportive care or with dose modification if Grade 2 or higher (see section 4.2).

Hepatotoxicity

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

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.

Women of childbearing potential must use highly effective contraception while taking NINLARO and for 90 days after stopping treatment (see sections 4.5 and 4.6). 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 seizure, 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 sections 4.5 and 5.2). 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 ixazomib with clarithromycin, a strong CYP3A inhibitor, 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%. Therefore, no dose modification is required for ixazomib with co-administration of strong CYP3A inhibitors.

Co-administration of ixazomib 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 pharmacokinetic (PK) analysis. Therefore, no dose modification is required for ixazomib with co-administration of strong CYP1A2 inhibitors.

CYP inducers

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

Effect of ixazomib on other medicinal products

Ixazomib is not a reversible or 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. Ixazomib 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 or hepatic OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Ixazomib 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

As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the SmPC for these medicinal products for additional information on fertility, pregnancy and lactation.

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 not recommended 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 not recommended 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.

There are no data for the use of NINLARO in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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 SmPC.

Breast-feeding

It is unknown whether NINLARO or its metabolites are excreted in human milk. No animal data are available. A risk to newborns/infants cannot be excluded and therefore breast-feeding should be discontinued.

NINLARO will be given in combination with lenalidomide and breast-feeding should be stopped because of the use of lenalidomide.

Fertility

Fertility studies have not been conducted with NINLARO (see section 5.3).

4.7 Effects on ability to drive and use machines

NINLARO has minor influence on the ability to drive or 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 SmPC for these medicinal products for additional undesirable effects.

Summary of the safety profile

The most frequently reported adverse reactions (≥ 20%) across 360 patients treated each within the NINLARO and placebo regimens in the pivotal clinical trial were diarrhoea (42% vs. 36%), constipation (34% vs. 25%), thrombocytopenia (28% vs. 14%), peripheral neuropathy (28% vs. 21%), nausea (26% vs. 21%), peripheral oedema (25% vs. 18%), vomiting (22% vs. 11%), and back pain (21% vs. 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhoea (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 adverse drug reactions 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) in the pivotal clinical trial

System organ class / Adverse reaction	Adverse reactions (all grades)	Grade 3 adverse reactions	Grade 4 adverse reactions
Infection and infestation			
Upper respiratory tract infection	Very common	Uncommon	
Herpes zoster	Common	Uncommon	
Blood and lymphatic system disorders			
Thrombocytopenia*	Very common	Very common	Common
Neutropenia	Very common	Very common	Common
Nervous system disorders			
Peripheral neuropathies*	Very common	Common	
Gastrointestinal disorders			
Diarrhoea	Very common	Common	
Nausea	Very common	Common	
Vomiting	Very common	Common	
Constipation	Very common	Uncommon	
Skin and subcutaneous tissue disorders			
Rash*	Very common	Common	
Musculoskeletal and connective tissue disorders			
Back pain	Very common	Uncommon	
General disorders and administration site conditions			
Oedema peripheral	Very common	Common	

Note: Adverse drug reactions included as preferred terms are based on MedDRA version 16.0.
*Represents a pooling of preferred terms

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 NINLARO regimen.

Thrombocytopenia

Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5,000/mm3 during treatment. Thrombocytopenia resulted in discontinuation of one or more of the three medicinal products in < 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Thrombocytopenia 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 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen.

Rash

Rash occurred in 19% of patients in the NINLARO regimen compared to 11% of patients in the placebo regimen. The most common type of rash reported in both regimens was macula-papular and macular rash. Grade 3 rash was reported in 3% of patients in the NINLARO regimen compared to 1% 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 NINLARO regimen compared to 21% of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. 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%). Peripheral neuropathy resulted in discontinuation of one or more of the three medicinal products in 1% of patients in both regimens.

Eye Disorders

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.

Other adverse reactions

Outside of the Phase 3 study, the following serious adverse reactions 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.

In the pivotal Phase 3 trial, the following adverse reactions occurred with a similar rate between the NINLARO and placebo regimens: fatigue (28% vs. 26%), neutropenia (30% vs. 27%), decreased appetite (13% vs. 9%), hypotension (5% vs. 4%), heart failure (4% vs. 3%), arrhythmia (13% each), and liver impairment including enzyme changes (6% vs. 5%).

The frequency of severe (Grade 3-4) events of hypokalaemia was higher in the NINLARO regimen (4%) than the placebo regimen (1%).

Fungal and viral pneumonia resulting in fatal outcome were rarely reported in patients given the NINLARO, lenalidomide and dexamethasone combination.

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.

4.9 Overdose

There is no known specific antidote for NINLARO overdose. Clinical data is limited but doses up to 12 mg have been reported in the randomized controlled trial. In the event of an overdose, monitor the patient for adverse reactions (section 4.8) and provide appropriate supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX50

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 NINLARO in combination with lenalidomide and dexamethasone was evaluated in an international randomized, 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 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. 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 NINLARO regimen.

Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide SmPC. 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 SmPC. 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.

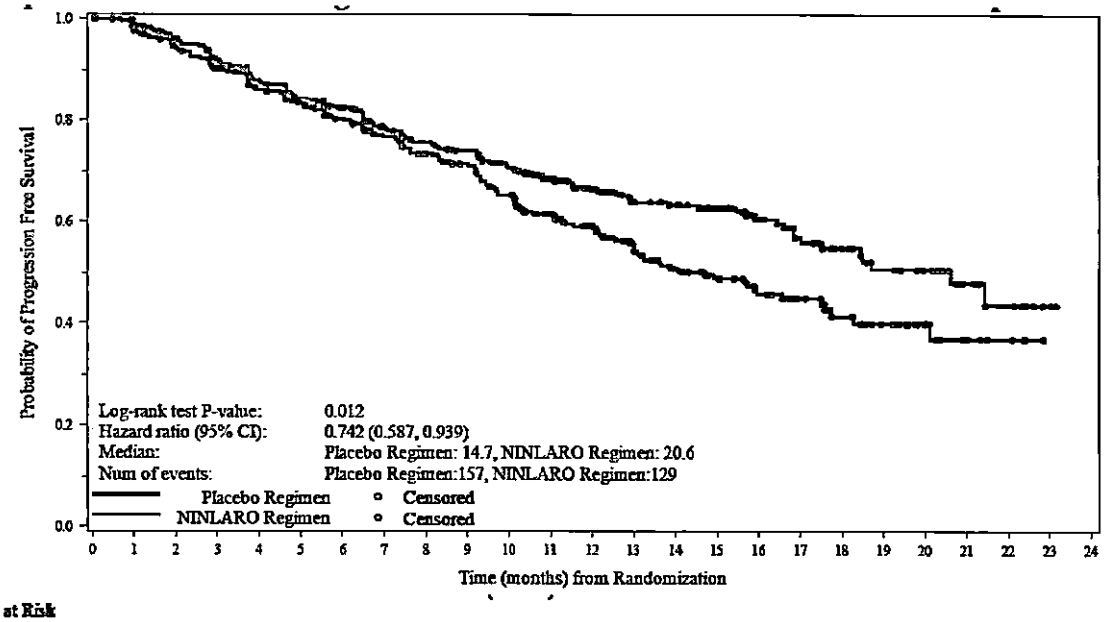
The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central laboratory results. Response was assessed every 4 weeks until disease 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 summarized in Table 4 and Figure 1. The improvement in PFS in the NINLARO regimen was supported by improvements in overall response rate.

Table 4: Progression Free Survival and Response 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
p-value*	0.012	
Hazard Ratio† (95% CI)	0.74 (0.59, 0.94)	
Overall Response Rate‡, 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 NINLARO regimen.
‡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

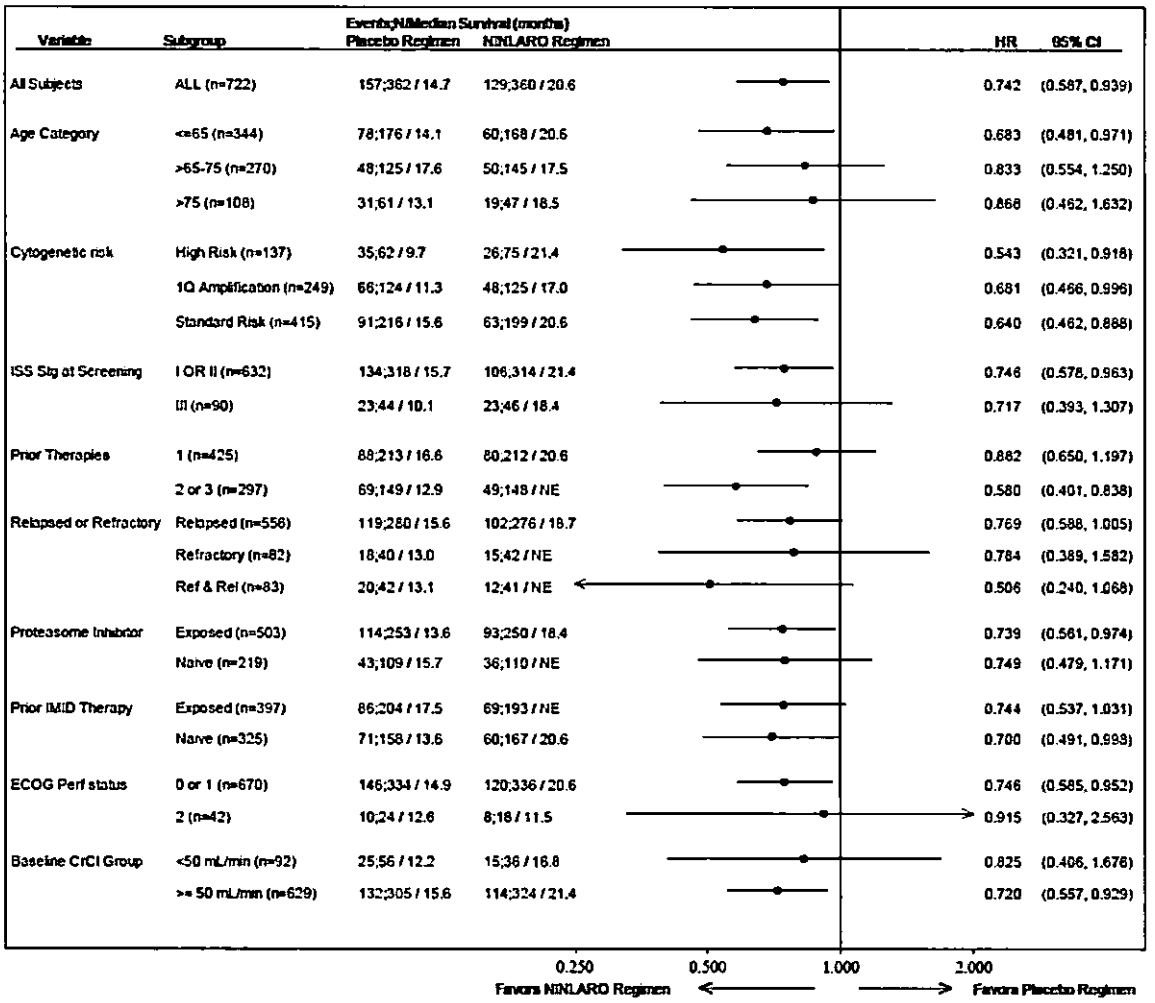


Number of Patients at Risk																								
Placebo Regimen	362	340	325	308	288	274	254	237	218	203	188	157	130	101	83	71	58	46	31	22	15	5	3	0	0
NINLARO Regimen	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	93	72	58	44	34	26	14	9	1	0

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 this analysis, 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.

As multiple myeloma is a heterogeneous disease, benefit may vary across subgroups in the Phase 3 study (C16010) (see Figure 2).

Figure 2: Forest plot of progression-free survival in subgroups



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 NINLARO 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).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with NINLARO in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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).

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).

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).

Age, gender, race

There was no clinically meaningful effect of age (23-91 years), sex, body surface area (1.2-2.7 m2), 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 NINLARO 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 0.2 mg/kg (4 mg/m2). 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.

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

See expiry date on product packaging

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

NINLARO 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. MARKETING AUTHORISATION HOLDER

Imported by: Takeda (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Mar 2017 (Ref: EU SmPC 12/2016)
Submission date: May 2017