NINLARO™
(Ixazomib)

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 gelatin hard capsule, marked “Takeda” on the cap and “2.3 mg” on the body withblack ink.

NINLARO 3 mg hard capsules

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

NINLARO 4 mg hard capsules

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma after receiving 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 themanagement 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 a28-day treatment cycle.

The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a28-day treatment cycle.

Dosing schedule: Ixazomib 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
Ixazomib	✔		✔		✔			
Lenalidomide	✔	✔ Daily	✔	✔ Daily	✔	✔ Daily		
Dexamethasone	✔		✔		✔		✔	

✔ = intake of medicinal product

For additional information regarding lenalidomide and dexamethasone, refer to the Summary ofProduct Characteristics (SmPC) for these medicinal 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 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 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 section 5.1).

Delayed or missed doses

In the event that a 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 nextscheduled 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 dosingat the time of the next scheduled dose.

Dose modifications

The ixazomib dose reduction steps are presented in Table 1 and the dose modification guidelines areprovided in Table 2.

Table 1: Ixazomib dose reduction steps

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

*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 ixazomib 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 ixazomib in combination with lenalidomide and dexamethasone

Haematological toxicities	**Recommended actions**
Thrombocytopenia (platelet count)	
Platelet count < 30,000/mm^3	• Withhold ixazomib and lenalidomide until platelet count ≥ 30,000/mm^3. • Following recovery, resume lenalidomide at the next lower dose according to its SmPC and resume ixazomib at its most recent dose. • If platelet count falls to < 30,000/mm^3 again, withhold ixazomib and lenalidomide until platelet count ≥ 30,000/mm^3. • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*
Neutropenia (absolute neutrophil count)	
Absolute neutrophil count < 500/mm^3	• Withhold ixazomib and lenalidomide until absolute neutrophil count is ≥ 500/mm^3. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume ixazomib at its most recent dose. • If absolute neutrophil count falls to < 500/mm^3 again, withhold ixazomib and lenalidomide until absolute neutrophil count is ≥ 500/mm^3. • Following recovery, resume ixazomib 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 ixazomib and lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*
Grade 4	Discontinue treatment regimen.

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

Peripheral neuropathy	
Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy	• Withhold ixazomib until peripheral neuropathy recovers to ≤ Grade 1 without pain or patient's baseline. • Following recovery, resume ixazomib at its most recent dose.
Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming ixazomib. • Following recovery, resume ixazomib 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 ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming ixazomib. • If attributable to ixazomib, resume ixazomib at the next lower dose following recovery.

*For additional occurrences, alternate dose modification of lenalidomide and ixazomib
†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 riskof herpes zoster reactivation. Patients included in studies with ixazomib who received antiviral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receiveprophylaxis.

Thromboprophylaxis is recommended in patients being treated with ixazomib in combination with lenalidomide and dexamethasone, and should be based on an assessment of the patient's underlyingrisks 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 ixazomib is required for patients over 65 years of age.

Discontinuations in patients > 75 years of age were reported in 13 patients (28%) in the ixazomib regimen and 10 patients (16%) in the placebo regimen. Cardiac arrhythmias in patients > 75 years ofage were observed in 10 patients (21%) in the ixazomib regimen and 9 patients (15%) in the placeboregimen.

Hepatic impairment

No dose adjustment of ixazomib 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 ixazomib 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 severerenal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease (ESRD) requiring dialysis. Ixazomib is not dialyzable and, therefore, can be administered without regard to the timing ofdialysis (see section 5.2).

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

Paediatric population

The safety and efficacy of ixazomib in children below 18 years of age have not been established. Nodata are available.

Method of administration

Ixazomib is for oral use.

Ixazomib should be taken at approximately the same time on Days 1, 8, and 15 of each treatment cycleat 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 ixazomib is administered in combination with lenalidomide and dexamethasone, refer to the SmPCfor these medicinal products for additional contraindications.

4.4 Special warnings and precautions for use

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

Thrombocytopenia

Thrombocytopenia has been reported with ixazomib (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 nextcycle (see section 4.8).

Platelet counts should be monitored at least monthly during ixazomib 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 transfusionsas per standard medical guidelines.

Gastrointestinal toxicities

Diarrhoea, constipation, nausea and vomiting have been reported with ixazomib, occasionallyrequiring 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 ofsevere gastrointestinal events, monitoring of serum potassium level is recommended.

Peripheral neuropathy

Peripheral neuropathy has been reported with ixazomib (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 ixazomib (see section 4.8). The patient should be evaluated for underlying causes and provide supportive care, as necessary. The dose of dexamethasone should beadjusted per its prescribing information or ixazomib for Grade 3 or 4 symptoms (see section 4.2).

Cutaneous reactions

Rash has been reported with ixazomib (see section 4.8). Rash should be managed with supportive careor with dose modification if Grade 2 or higher (see section 4.2). Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported with ixazomib (see section 4.8). If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, discontinue ixazomib.

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 ixazomib (see section 4.8). Hepatic enzymesshould 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 ixazomib. If ixazomib is used during pregnancy or if the patient becomes pregnant while taking ixazomib, the patient should beapprised of the potential hazard to the foetus.

Women of childbearing potential must use highly effective contraception while taking ixazomib 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 ixazomib.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 ixazomib.

Strong CYP3A inducers

Strong inducers may reduce the efficacy of ixazomib, therefore the concomitant use of strong CYP3Ainducers 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 by4% 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 hepaticOATPs. 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 ixazomib 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 ixazomib 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. Ixazomib is not recommended in women of childbearingpotential not using contraception.

When ixazomib 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

Ixazomib is not recommended during pregnancy as it can cause foetal harm when administered to apregnant woman. Therefore, women should avoid becoming pregnant while being treated with ixazomib.

There are no data for the use of ixazomib in pregnant women. Studies in animals have shownreproductive toxicity (see section 5.3).
Ixazomib is given in combination with lenalidomide. Lenalidomide is structurally related tothalidomide. 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 fulfilledfor 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 ixazomib or its metabolites are excreted in human milk. No animal data areavailable. A risk to newborns/infants cannot be excluded and therefore breast-feeding should be discontinued.

Ixazomib will be given in combination with lenalidomide and breast-feeding should be stoppedbecause of the use of lenalidomide.

Fertility

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

4.7 Effects on ability to drive and use machines

Ixazomib has minor influence on the ability to drive or use machines. Fatigue and dizziness have beenobserved 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 ixazomib is administered in combination with lenalidomide and dexamethasone, refer to the SmPCfor these medicinal products for additional undesirable effects.

Summary of the safety profile

The safety profile of NINLARO is based on available clinical trial data and post-marketing experienceto date. Frequencies of adverse reactions described below and in Table 3 have been determined based on data generated from clinical studies.

Unless otherwise noted, 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%), thrombocytopenia (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%), peripheral oedema (24% vs. 19%),vomiting (23% vs. 12%) and bronchitis (20% vs 15%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (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 decreasingseriousness.

Table 3: Adverse reactions in patients treated with ixazomib 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			
Thrombocytopenia*	Very common	Very common	Common
Neutropenia*	Very common	Very common	Common
Thrombotic microangiopathy	Rare		Rare
Thrombotic thrombocytopenic purpura†	Rare	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	
Gastrointestinal 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	
Musculoskeletal and connective tissue disorders			
Back pain	Very common	Uncommon	
General disorders and administration site conditions			
Oedema peripheral	Very common	Common	

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 ≤ 3% of patients in the ixazomib regimen.

Thrombocytopenia

Two percent of patients in both the ixazomib regimen and 1% of patients 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. Thrombocytopenia 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. 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 2% of patientsin 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 placeboregimen. 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 patientsin 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 in2% 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 (< 1%). 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 4% in the placebo regimen), dry eye (6% in the ixazomib regimen and 1% in the placebo regimen), conjunctivitis (8% inthe 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 in 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% each), 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(7%) than the placebo regimen (2%).

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

Postmarketing

Clinically significant adverse drug reactions are listed here if they have not been reported above.
Blood and lymphatic system disorders: thrombotic microangiopathy
Immune system disorders: anaphylactic reactions
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema

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 professionals are asked to report any suspected adverse reactions through email : AE.Indonesia@takeda.com and/ or the national reporting system (https://e-meso.pom.go.id).

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 (section 4.8) and provide appropriate supportive care. Ixazomib isnot dialyzable (see section 5.2).

Overdoses were most common in patients starting treatment with NINLARO. The importance ofcarefully 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

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, 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 preferentiallybinds 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 microenvironmentincluding 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 modelbased 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 hadreceived 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 priorto 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 SmPC. Concomitant medicinal products, such as antiemetic, antiviral, and antihistaminemedicinal products were given to patients at the physician'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 1through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients with renalimpairment received a starting dose of lenalidomide according to its SmPC. Treatment continued untildisease 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 and12% 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.

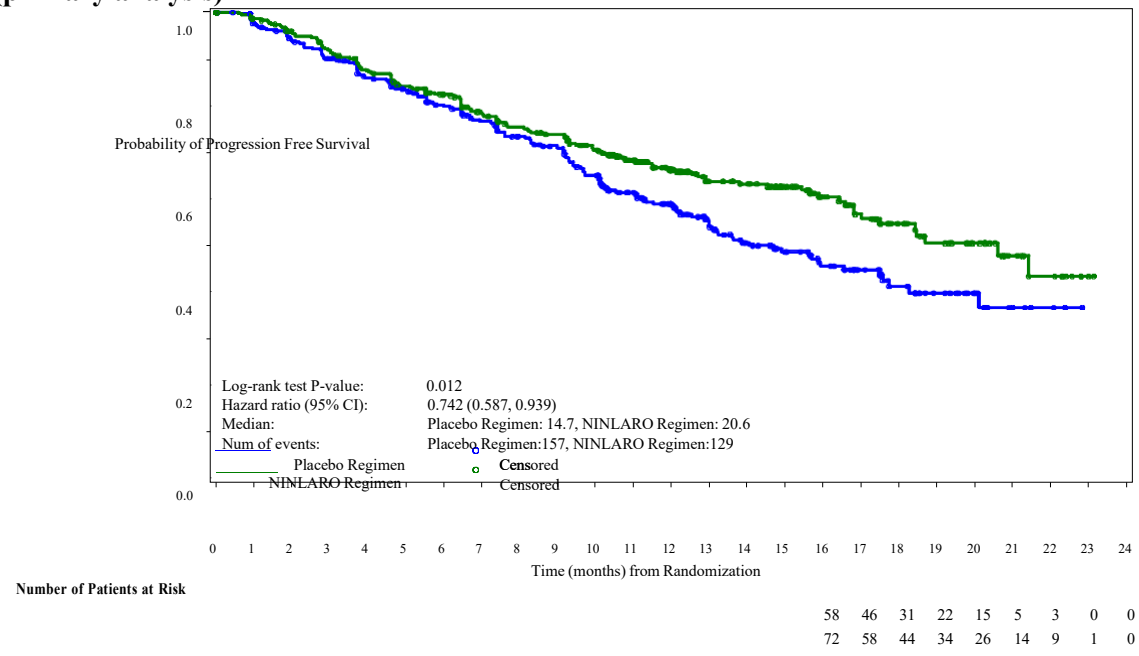
The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central laboratory results. Response was assessed every4 weeks until disease 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 wassupported 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, primary analysis)

	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‡, 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.
‡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 (primary analysis)



Placebo Regimen	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71
NINLARO Regimen	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95

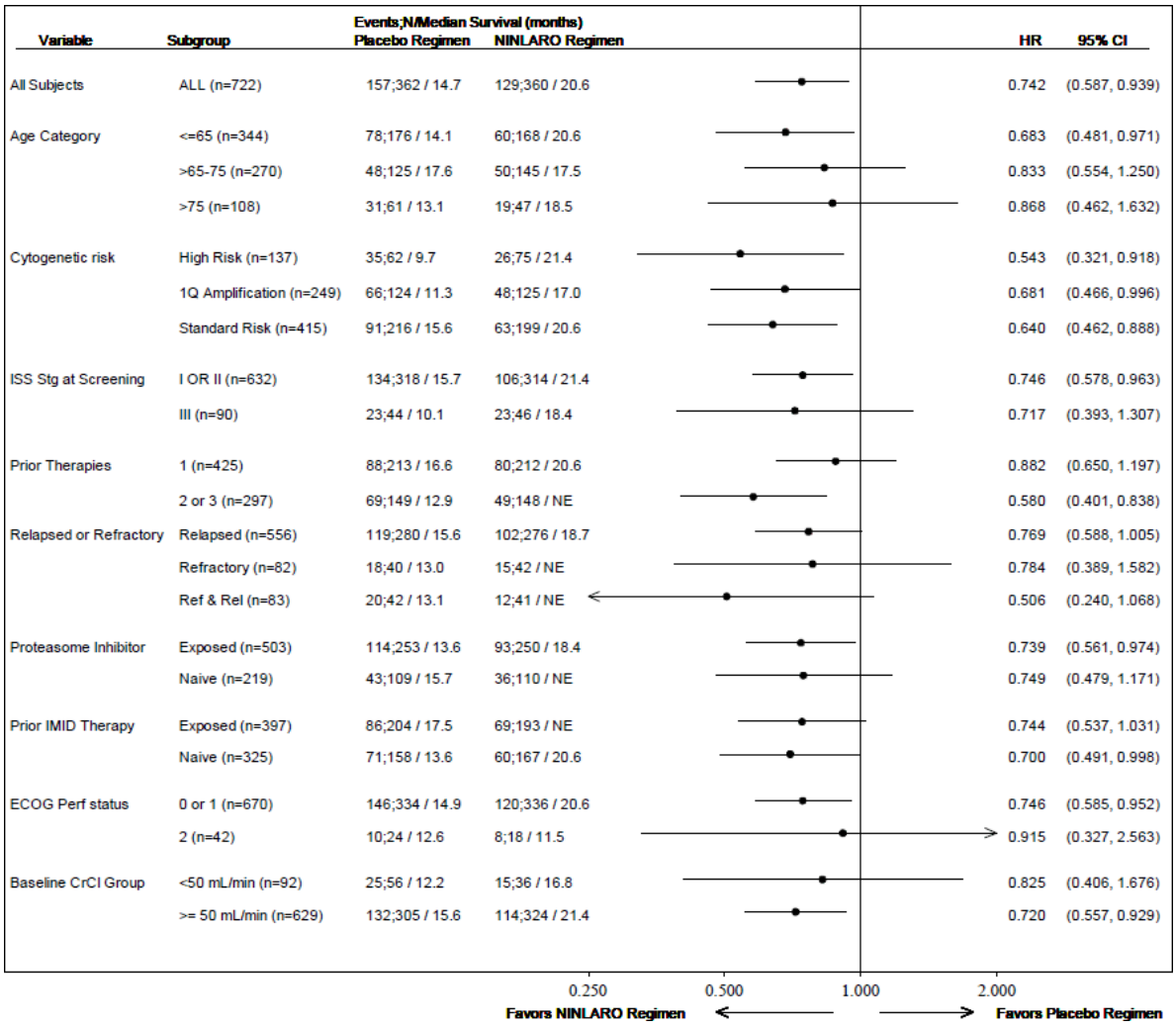
A second, non-inferential, PFS analysis was conducted with a median follow up of 23 months. At this analysis, estimated median PFS was 20 months inthe ixazomib regimen and 15.9 months in the placebo regimen (HR=0.82 [95% CI (0.67, 1.0)]) in theITT population. For patients with one prior therapy, the 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) witha 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) (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 impairmentat 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 confirmedvery good partial response.

Quality of life as assessed by global health scores (EORTC QLQ-C30 and MY-20) was maintainedduring 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 withixazomib 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 approximatelyone hour after dosing. The mean absolute oral bioavailability is 58%. Ixazomib AUC increases in adose 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 administrationafter 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 expectedto 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 tooverall metabolism. At concentrations exceeding those observed clinically, ixazomib was metabolizedby 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 observedwith 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% ofthe 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 anyAST) 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 withnormal 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 PKanalysis.

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 patientswith 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 m^2), orrace 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 inhuman peripheral blood lymphocytes. However, ixazomib was negative in an *in vivo* comet assay inmice, 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 andat 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 organsincluded 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/m^2). 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 telemetereddogs 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

The secondary packaging for ixazomib consists of a wallet card made of solid bleached sulfate (SBS) paperboard. Each individual wallet card contains three blisters which have been sealed to the wallet card and is not detachable. The wallet card containing three blisters and one patient information leaflet (PI) is placed into an outer final paperboard 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 soapand water.

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

Box, 1 wallet @ 1 blister @ 3 hard capsules

Registration number:
DKI2331500301A1 (NINLARO 2.3 mg)
DKI2331500301B1 (NINLARO 3 mg)
DKI2331500301C1 (NINLARO 4 mg)

HARUS DENGAN RESEP DOKTER

Marketing Authorization Holder :

PT Takeda Indonesia
Bekasi, Indonesia

Manufactured by Haupt Pharma Amareg GmbH, Regensburg Germany;
Primary packed by AndersonBrecon (UK) Limited,Talgarth, UK;
Secondary packed by AndersonBrecon (UK) Limited, Hereford, UK;
Released by Takeda Ireland Limited, Grange Castle, Ireland;
Imported by PT. Takeda Indonesia, Bekasi - Indonesia

Based on EU SmPC and Ixazomib CCDS ver6 dated 6 Jul 2023.

Brosur : Informasi untuk pasien

NINLARO 2.3 mg Kapsul
NINLARO 3 mg Kapsul
NINLARO 4 mg Kapsul
Zat aktif : ixazomib

Pada obat ini harus dilakukan pemantauan tambahan. Hal ini untuk identifikasi yang cepat terhadap informasi keamanan terbaru. Anda dapat membantu dengan melaporkan efek samping yang Anda alami. Lihat pada akhir bagian 4 tentang bagaimana melaporkan efek samping.

Baca brosur ini dengan seksama sebelum Anda mulai menggunakan obat ini karena tercantum informasi penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, silakan tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, bahkan jika gejalanya sama dengan Anda.
- Jika terjadi efek samping, atau jika Anda menderita efek samping yang tidak tercantum dalam brosur ini, bicarakan dengan dokter atau apoteker Anda. Lihat bagian 4.

Informasi yang tercantum dalam brosur ini :

1. Apakah NINLARO itu dan apa kegunaannya

NINLARO adalah obat kanker yang mengandung ixazomib, suatu penghambat *proteasome*.

Ninlaro digunakan sebagai pengobatan kanker sumsum tulang yang disebut *multiple myeloma*. Zat aktif ixazomib bekerja dengan menghambat kerja *proteasome*, yaitu struktur di dalam sel yang berfungsi memecah protein dan berperan penting untuk kelangsungan hidup sel. Karena sel mieloma menghasilkan banyak protein, maka dengan menghambat kerja proteasome dapat membunuh sel-sel kanker.

NINLARO digunakan untuk :
- Pengobatan orang dewasa dengan *multiple myeloma*. NINLARO akan diberikan pada Anda bersamaan dengan lenalidomide dan dexamethasone, yaitu obat-obatan lain yang digunakan juga untuk pengobatan *multiple myeloma* yang kambuh atau refrakter setelah menerima setidaknya 1 pengobatan sebelumnya.

Apa yang dimaksud dengan *multiple myeloma*
Multiple myeloma adalah kanker darah yang mempengaruhi tipe sel yang disebut sel plasma. Sel plasma adalah sel darah yang memproduksi protein yang melawan infeksi. Pasien dengan *multiple myeloma* memiliki sel plasma yang bersifat kanker, juga disebut sel mieloma yang dapat merusak

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tulang. Protein yang diproduksi oleh sel mieloma dapat merusak ginjal. Pengobatan untuk *multiple myeloma* membunuh sel mieloma dan mengurangi gejala penyakit.

2. Yang perlu Anda ketahui sebelum menggunakan NINLARO

JANGAN mengkonsumsi NINLARO jika Anda :

- alergi terhadap ixazomib atau terhadap salah satu bahan tambahan dari obat ini (tercantum dalam bagian 6)

Peringatan dan Perhatian

Bicarakan dengan dokter, apoteker atau perawat sebelum minum NINLARO jika :

- Anda memiliki riwayat perdarahan
- Anda mengalami mual, muntah, dan diare yang persisten
- Anda memiliki riwayat masalah saraf, termasuk kesemutan dan mati rasa.
- Anda memiliki riwayat bengkak
- Anda memiliki ruam yang persisten
- Anda memiliki masalah hati atau ginjal sehingga dosis anda harus disesuaikan
- Anda memiliki atau pernah memiliki riwayat kerusakan pembuluh darah terkecil yang dinamakan mikroangiopati trombotik atau purpura trombositopenia trombotik. Katakan pada dokter jika anda mengalami lelah, demam, memar, perdarahan, berkurangnya buang air kecil, bengkak, bingung, hilang penglihatan dan kejang.
- Nekrolisis epidermal toksik (sindrom Stevens-Johnson dalam tingkat yang lebih parah). Suatu reaksi kulit yang umumnya terjadi akibat obat-obatan yang menimbulkan lepuh pada kulit, dengan penampakan kulit seperti terbakar yang menyeluruh.

Dokter Anda akan memeriksa dan memonitor Anda dengan ketat selama pengobatan. Sebelum dan selama pengobatan dengan Ninlaro, dokter Anda akan melakukan pengujian darah untuk memastikan bahwa Anda memiliki sel darah yang cukup memadai.

Anak-anak dan Remaja

NINLARO tidak dianjurkan untuk pemakaian pada anak-anak dan remaja berumur dibawah 18 tahun.

Mengkonsumsi obat-obatan lain dan NINLARO

Informasikan kepada Dokter jika Anda sedang minum obat lain, jika Anda sudah mengkonsumsi obat lain saat ini, atau jika Anda baru mulai mengkonsumsi obat lain. Hal ini termasuk obat-obat lain yang Anda peroleh tanpa resep dokter, seperti vitamin atau herbal. Hal ini karena obat lain dapat mempengaruhi cara kerja NINLARO. Secara khusus, beritahukan dokter, apoteker atau perawat jika Anda minum obat-obat lain berikut ini : karbamazepin, fenitoin, rifampicin dan St. John's wort (Hypericum perforatum). Obat-obatan ini harus dihindari karena dapat mengurangi efektifitas NINLARO.

Kehamilan dan menyusui

NINLARO tidak dianjurkan selama kehamilan karena mungkin membahayakan janin Anda. Hentikan menyusui ketika mengkonsumsi NINLARO.

Hindari rencana hamil atau menyusui ketika sedang dalam pengobatan dengan NINLARO. Jika Anda hamil atau menyusui, berpikir bahwa Anda mungkin hamil atau merencanakan kehamilan, tanyakan dokter atau apoteker Anda untuk saran sebelum mengkonsumsi obat ini.

Jika Anda seorang wanita yang berpotensi melahirkan anak atau pria yang berpotensi memiliki anak, Anda harus menggunakan kontrasepsi yang efektif selama dan 90 hari setelah pengobatan. Wanita yang menggunakan kontrasepsi hormonal harus menggunakan kontrasepsi tambahan. Beritahukan dokter Anda segera apabila Anda atau pasangan Anda hamil ketika menggunakan NINLARO.

Oleh karena NINLARO diberikan dalam kombinasi dengan lenalidomide, Anda harus mengikuti program pencegahan kehamilan karena lenalidomide dapat membahayakan janin.

Baca brosur untuk lenalidomide dan dexamethasone untuk tambahan informasi kehamilan dan menyusui.

Mengemudi dan menggunakan mesin

NINLARO mungkin mempengaruhi kemampuan Anda dalam mengemudi dan menjalankan mesin. Anda mungkin merasa lelah dan pusing selama pengobatan NINLARO. Jangan mengemudi atau menjalankan mesin bila Anda mengalami efek samping ini.

3. Bagaimana cara menggunakan NINLARO

NINLARO harus diresepkan oleh dokter yang berpengalaman dalam pengobatan *multiple myeloma*. Selalu minum obat ini tepat sesuai dengan yang telah diinformasikan oleh dokter atau apoteker Anda.

NINLARO digunakan bersamaan dengan lenalidomide (obat yang mempengaruhi cara kerja sistem imun tubuh Anda) dan dexamethasone (obat anti inflamasi).

Dosis awal ixazomib yang direkomendasikan adalah 4 mg diberikan secara oral seminggu sekali pada Hari 1, 8, dan 15 dari siklus pengobatan 28 hari.

Dosis awal lenalidomide yang direkomendasikan adalah 25 mg diberikan setiap hari pada Hari 1 sampai 21 dari siklus pengobatan 28 hari.

Dosis awal deksametason yang direkomendasikan adalah 40 mg diberikan pada Hari 1, 8, 15, dan 22 dari siklus pengobatan 28 hari.

Jadwal Dosis : Pemberian NINLARO bersama dengan lenalidomide dan dexamethasone

✔ Minum Obat

Siklus 28-hari (Siklus 4 minggu)								
	Minggu 1		**Minggu 2**		**Minggu 3**		**Minggu 4**	
	Hari ke-1	Hari ke 2 - 7	Hari ke-8	Hari ke 9 - 14	Hari ke-15	Hari ke 16 - 21	Hari ke-22	Hari ke 23 - 28
NINLARO	✔		✔		✔			
Lenalidomide	✔	✔ Tiap hari	✔	✔ Tiap hari	✔	✔ Tiap hari		
Dexamethasone	✔		✔		✔		✔	

Sebaiknya Anda membaca brosur kedua obat lainnya untuk informasi lebih lanjut mengenai cara penggunaan dan efeknya.

Bila anda bermasalah dengan hati dan ginjal, dokter mungkin memberikan resep NINLARO Kapsul isi 3 mg.
Bila anda mengalami efek samping, dokter mungkin memberikan resep NINLARO Kapsul isi 3 mg atau 2,3 mg.
Dokter mungkin juga menyesuaikan dosis obat lainnya.

Bagaimana dan kapan pemberian NINLARO

- Minum NINLARO minimal 1 jam sebelum makan atau 2 jam setelah makan.
- Telan kapsul seluruhnya dengan air. Jangan menggerus, mengunyah atau membuka kapsul.
- Jangan biarkan isi kapsul menyentuh kulit Anda. Bila secara tidak sengaja serbuk kapsul menyentuh kulit Anda, segera cuci dengan sabun dan bilas dengan air. Apabila kapsul pecah/terbuka, bersihkan serbuk kapsul sedemikian rupa agar serbuk tidak bertebaran di udara.

Jika Anda menelan NINLARO melebihi yang seharusnya
Jika Anda menelan NINLARO melebihi yang seharusnya, beritahukan dokter Anda atau segera ke rumah sakit terdekat. Bawalah obat-obatan tersebut.

Masa pengobatan dengan NINLARO
Anda harus melanjutkan pengobatan hingga dokter memberitahukan anda untuk menghentikan pengobatan.

Jika Anda lupa minum NINLARO
Jika ada dosis NINLARO yang lupa diminum atau tertunda, Anda harus menelannya sepanjang dosis obat yg berikutnya masih lebih dari 3 hari atau 72 jam kedepan. Jangan minum dosis obat yang lupa diminum bila jadwal dosis berikutnya sudah dalam 3 hari atau 72 jam.

Jika Anda muntah setelah menelan dosis obat, jangan minum dosis tambahan. Minumlah dosis berikutnya seperti biasa sesuai jadwalnya.
Jika Anda ingin menanyakan lebih lanjut tentang penggunaan obat ini, hubungi dokter atau apoteker anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, NINLARO dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Beritahukan dokter atau apoteker terdekat jika anda mengalami :
Efek samping sangat umum (terjadi pada lebih dari 1 dari 10 orang)

- Penurunan jumlah trombosit (trombositopenia) yang mungkin meningkatkan resiko hidung berdarah (mimisan) dan mudah memar
- Mual, muntah dan diare
- Mati rasa, kesemutan atau rasa terbakar pada tangan atau kaki (neuropati perifer)
- Pembengkakan pada tungkai atau kaki (edema perifer)
- Ruam kulit yang mungkin terasa gatal dan di beberapa area atau di seluruh tubuh

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Efek samping yang jarang terjadi (terjadi pada lebih dari 1 dari 1000 orang) :

- ruam kulit yang parah seperti benjolan merah ke ungu (sindrom Sweet) atau ruam yang mengelupas dan sariawan (sindrom Stevens Johnson)
- kelemahan otot, hilangnya rasa pada jari-jari kaki dan kaki, atau hilangnya gerakan tungkai (mielitis transversal)
- perubahan penglihatan, perubahan status mental, atau kejang (sindrom ensefalopati posterior reversibel)
- kematian cepat sel kanker yang dapat menyebabkan pusing, berkurangnya buang air kecil, kebingungan, muntah, mual, bengkak, sesak napas, atau gangguan irama jantung (sindrom lisis tumor)
- kondisi darah langka akibat pembekuan darah yang dapat menyebabkan kelelahan, demam, memar, pendarahan misalnya pendarahan hidung, berkurangnya buang air kecil, bengkak, kebingungan, kehilangan penglihatan, dan kejang (mikroangiopati trombotik, purpura trombositopenik trombotik)

Efek samping lain yang mungkin timbul

Beritahukan dokter atau apoteker jika Anda jika efek samping dibawah ini bertambah parah.

Efek samping yang sangat umum dapat mempengaruhi lebih dari 1 dari 10 orang:

- sembelit
- sakit punggung
- gejala seperti pilek (infeksi saluran pernapasan bagian atas)
- merasa lelah atau lemah (kelelahan)
- penurunan sel darah putih yang disebut neutrofil (neutropenia) yang dapat meningkatkan risiko infeksi
- tidak merasa ingin makan (nafsu makan menurun)
- detak jantung tidak teratur (aritmia)
- kondisi penglihatan termasuk penglihatan kabur, mata kering dan mata merah (konjungtivitis)

Efek samping yang umum dapat mempengaruhi hingga 1 dari 10 orang:

- pengaktifan kembali virus cacar air (herpes zoster) yang dapat menyebabkan ruam kulit dan nyeri (herpes zoster)
- penurunan tekanan darah (hipotensi)
- sesak napas atau batuk terus-menerus atau mengi (gagal jantung)
- perubahan warna kuning pada mata dan kulit (penyakit kuning yang bisa menjadi gejala kerusakan hati)
- rendahnya kadar kalium dalam darah (hipokalemia)

Berikut ini reaksi efek samping obat, jika belum dilaporkan di atas :

- Mikroangiopati trombotik (suatu kondisi klinis yang ditandai dengan adanya penurunan jumlah sel darah merah akibat adanya penghancuran sel darah merah tersebut, jumlah trombosit yang rendah, dan kerusakan organ akibat pembentukan bekuan darah mikroskopis pada pembuluh darah kapiler & arteri kecil).
- Reaksi anafilaksis (reaksi alergi berat dan terjadi secara tiba-tiba setelah tubuh terpapar zat pemicu alergi).
- Sindrom Stevens-Johnson (suatu reaksi kulit yang sangat jarang terjadi, yang bersifat akut dan fatal, yang ditandai dengan timbulnya kemerahan & lepuh pada kulit).

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- Nekrolisis epidermal toksik (sindrom Stevens-Johnson dalam tingkat yang lebih parah). Suatu reaksi kulit yang umumnya terjadi akibat obat-obatan yang menimbulkan lepuh pada kulit, dengan penampakan kulit seperti terbakar yang menyeluruh.
- Angioedema (pembengkakan pada lapisan di bawah kulit atau di bawah selaput lendir yang dapat timbul pada mata, bibir, saluran napas, atau bagian tubuh lainnya).

Pelaporan efek samping
Jika Anda mengalami efek samping, informasikan kepada dokter, apoteker, atau suster Anda. Termasuk efek samping lain yang tidak tercantum dalam leaflet ini. Anda juga dapat melaporkan efek samping ini langsung ke sistem pelaporan melalui email berikut :AE.Indonesia@takeda.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi tambahan terkait profil keamanan dari obat ini.

5. Bagaimana cara penyimpanan NINLARO

Jauhkan dari jangkauan dan penglihatan anak-anak.

Jangan gunakan NINLARO melewati tanggal kadaluwarsa yang tertera pada blister, catch cover dan karton setelah "EXP". Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan yang bersangkutan.

Jangan simpan diatas 30°C. Jangan dibekukan.
Simpan blister dalam kemasan aslinya untuk melindungi dari kelembaban.
Jangan keluarkan kapsul sampai saat jadwal anda menelan dosisnya.
Jangan gunakan obat jika ada kerusakan pada kemasan obat.

Obat tidak boleh dibuang melalui saluran air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat yang tidak digunakan lagi. Langkah ini akan membantu perlindungan lingkungan.

6. Informasi kemasan dan informasi lain

Apa saja kandungan NINLARO

NINLARO 2,3 mg kapsul keras:
- Kandungan zat aktif adalah ixazomib. Tiap kapsul berisi 2,3 mg ixazomib (setara dengan 3,3 mg ixazomib citrate).
- Kandungan zat tambahan :
  - Di dalam kapsul : mikrokristalin selulosa, magnesium stearat dan talk
  - Cangkang kapsul mengandung : gelatin, titanium dioksida (E171) dan feri oksida merah (E172)
  - Tinta cetak kapsul mengandung : shellac, propilen glikol, kalium hidroksida dan feri oksida hitam (E172).

NINLARO 3 mg kapsul keras :
- Kandungan zat aktif adalah ixazomib. Tiap kapsul berisi 3 mg ixazomib (setara dengan 4,3 mg ixazomib citrate).
- Kandungan zat tambahan :
  - Di dalam kapsul : mikrokristalin selulosa, magnesium stearat dan talk

- Cangkang kapsul mengandung : gelatin, titanium dioksida (E171) dan feri oksida hitam (E172)
- Tinta cetak kapsul mengandung : shellac, propilen glikol, kalium hidroksida dan feri oksida hitam (E172).

NINLARO 4 mg kapsul keras :

- Kandungan zat aktif adalah ixazomib. Tiap kapsul berisi 4 mg ixazomib (setara dengan 5,7 mg ixazomib citrate).
- Kandungan zat tambahan :
  - Di dalam kapsul : mikrokristalin selulosa, magnesium stearat dan talk
  - Cangkang kapsul mengandung : gelatin, titanium dioksida (E171) dan feri oksida kuning (E172) dan feri oksida merah (E172)
  - Tinta cetak kapsul mengandung : shellac, propilen glikol, kalium hidroksida dan feri oksida hitam (E172).

Bagaimana bentuk dan kemasan NINLARO

NINLARO Kapsul keras 2,3 mg: Merah muda, ukuran 4, dengan tulisan "Takeda" di tutup kapsul dan "2,3 mg" di badan kapsul dengan tinta hitam.

NINLARO Kapsul keras 3 mg : Abu-abu muda, ukuran 4, dengan tulisan "Takeda" di tutup kapsul dan "3 mg" di badan kapsul dengan tinta hitam.

NINLARO kapsul keras 4 mg: Jingga muda, ukuran 3, dengan tulisan "Takeda" di tutup kapsul dan "4 mg" di badan kapsul dengan tinta hitam.

Tiap kemasan berisi 3 kapsul keras (1 dus tunggal berisi 1 blister yang terbungkus dalam wallet blister. Tiap blister berisi 3 kapsul keras).

No Registrasi : DKI2331500301A1 (NINLARO 2,3 mg)
No Registrasi : DKI2331500301B1 (NINLARO 3 mg)
No Registrasi : DKI2331500301C1 (NINLARO 4 mg)

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