1. NAME OF THE MEDICINAL PRODUCT

Ninlaro® Hard capsule 2.3mg
Ninlaro® Hard capsule 3mg
Ninlaro® Hard capsule 4mg

2. NAME AND STRENGTH OF ACTIVE SUBSTANCES

Ninlaro is available in the following capsule strengths:

- 4mg: Ninlaro 4 mg hard capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.
- 3 mg: Ninlaro 3 mg hard capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.
- 2.3 mg: Ninlaro 2.3 mg hard capsules contain 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.

and the following excipients:
Excipients: microcrystalline cellulose, talc and magnesium stearate.

3. PRODUCT DESCRIPTION

Ninlaro is supplied as immediate release hard gelatin capsule and are distinguished both by color and dose specific imprinted markings on the body.

- 4mg: Light orange gelatin capsule imprinted with “Takeda” on the cap and “4.0mg” on the body in black ink.
- 3 mg: Light grey gelatin capsule imprinted with “Takeda” on the cap and “3.0 mg” on the body in black ink.
- 2.3 mg: Light pink gelatin capsule imprinted with “Takeda” on the cap and “2.3 mg” on the body in black ink.

4. INDICATION

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

5. DOSAGE AND ADMINISTRATION

5.1 Dosing and Administration Guidelines

Ninlaro in combination with lenalidomide and dexamethasone
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 through 21 of a 28-day treatment cycle.
The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle.

Table 1: Dosing Schedule for Ninlaro taken with Lenalidomide and Dexamethasone

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

Dexamethasone	✓		✓		✓		✓	

For additional information regarding lenalidomide and dexamethasone, refer to their prescribing information.
Ninlaro should be taken once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. Ninlaro should be taken at least one hour before or at least two hours after food [*see Clinical Pharmacology*]. The whole capsule should be swallowed with water. The capsule should not be crushed, chewed or opened.
If 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 the missed dose.
If vomiting occurs after taking a dose, the patient should not repeat the dose. The patient should resume dosing at the time of the next scheduled dose.

Prior to initiating a new cycle of therapy:

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

Treatment should be continued until disease progression or unacceptable toxicity.

Concomitant Medications
Consider antiviral prophylaxis in patients being treated with Ninlaro to decrease the risk of herpes zoster reactivation.

5.2 Dose Modification Guidelines

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

Table 2: Ninlaro Dose Reductions due to adverse reactions

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

*Recommended starting dose of 3 mg in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease requiring dialysis [*see Dosage and Administration*].

An alternating dose modification approach is recommended for Ninlaro and lenalidomide for thrombocytopenia, neutropenia, and rash as described in Table 3. Refer to the lenalidomide prescribing information if dose reduction is needed for lenalidomide.

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

Hematological Toxicities	**Recommended Actions**
Thrombocytopenia (Platelet Count)	
Platelet count less than 30,000/mm^3	• Withhold Ninlaro and lenalidomide until platelet count is at least 30,000/mm^3. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume Ninlaro at its most recent dose.

	• If platelet count falls to less than 30,000/mm^3 again, withhold Ninlaro and lenalidomide until platelet count is at least 30,000/mm^3. • Following recovery, resume Ninlaro at the next lower dose and resume lenalidomide at its most recent dose.*
Neutropenia (Absolute Neutrophil Count)	
Absolute neutrophil count less than 500/mm^3	• Withhold Ninlaro and lenalidomide until absolute neutrophil count is at least 500/mm^3. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume Ninlaro at its most recent dose. • If absolute neutrophil count falls to less than 500/mm^3 again, withhold Ninlaro and lenalidomide until absolute neutrophil count is at least 500/mm^3. • Following recovery, resume Ninlaro at the next lower dose and resume lenalidomide at its most recent dose.*
Non-Hematological Toxicities - Recommended Actions	
Rash	
Grade$^{\uparrow}$ 2 or 3	Withhold lenalidomide until rash recovers to Grade 1 or lower. • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information. • If Grade 2 or 3 rash occurs again, withhold Ninlaro and lenalidomide until rash recovers to Grade 1 or lower. • 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 or lower 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 or lower prior to resuming Ninlaro. • Following recovery, resume Ninlaro at the next lower dose.
Grade 4 Peripheral Neuropathy	Discontinue treatment regimen.
Other Non-Hematological Toxicities	
Other Grade 3 or 4 Non-Hematological Toxicities	• Withhold Ninlaro. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or Grade 1 or lower 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

5.3 Dosage in Patients with Hepatic Impairment

Reduce the starting dose of Ninlaro to 3 mg in patients with moderate (total bilirubin greater than 1.5-3 x ULN) or severe (total bilirubin greater than 3 x ULN) hepatic impairment [*see Use in Specific Populations and Clinical Pharmacology].*

5.4 Dosage in Patients with Renal Impairment

Reduce the starting dose of Ninlaro to 3 mg in patients with severe renal impairment (creatinine clearance less than 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 Use in Specific Populations and Clinical Pharmacology*].

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

6. CONTRAINDICATIONS

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

7. WARNINGS AND PRECAUTIONS

7.1 Thrombocytopenia

Thrombocytopenia has been reported with Ninlaro with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle.

Three percent of patients in the Ninlaro 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 ≤5000/mm^3 during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the Ninlaro regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs).The rate of platelet transfusions was 6% in the Ninlaro regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with Ninlaro. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications [*see Dosage and Administration*] and platelet transfusions as per standard medical guidelines.

7.2 Gastrointestinal Toxicities

Diarrhea, constipation, nausea, and vomiting, have been reported with Ninlaro, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the Ninlaro regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the Ninlaro regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms [*see Dosage and Administration*].

7.3 Peripheral Neuropathy

The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the Ninlaro regimen and 14% in the placebo regimen) and Grade 2 (8% in the Ninlaro regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions.

The most commonly reported reaction was peripheral sensory neuropathy (19% and 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 drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification [*see Dosage and Administration*].

7.4 Peripheral Edema

Peripheral edema was reported in 25% and 18% of patients in the Ninlaro and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the Ninlaro regimen and 13% in the placebo regimen) and Grade 2 (7% in the Ninlaro regimen and 4% in the placebo regimen).

Grade 3 peripheral edema was reported in 2% and 1% of patients in the Ninlaro and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or Ninlaro for Grade 3 or 4 symptoms [*see Dosage and Administration*].

7.5 Cutaneous Reactions

Rash has been reported with Ninlaro (see section 10). Rash should be managed with supportive care or with dose modification if Grade 2 or higher (see section 10). Stevens-Johnson syndrome has also been reported with ixazomib (see section 10). If Stevens-Johnson syndrome occurs, discontinue ixazomib.

7.6 Thrombotic Microangiopathy

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

7.7 Hepatotoxicity

Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with Ninlaro. Events of liver impairment have been reported (6% in the Ninlaro regimen and 5% in the placebo regimen).

Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms [*see Dosage and Administration*].

7.8 Embryo-Fetal Toxicity

Ninlaro can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Ninlaro. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Ninlaro. If Ninlaro is used during pregnancy or if the patient becomes pregnant while taking Ninlaro, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with Ninlaro and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception. [*see Use in Specific Populations and Nonclinical Toxicology*].

8. INTERACTIONS WITH OTHER MEDICAMENTS

Strong CYP3A Inducers

Avoid concomitant administration of Ninlaro with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort) [*see Clinical Pharmacology*].

Strong CYP3A Inhibitors
Co-administration of Ninlaro with clarithromycin did not result in a clinically meaningful change in the systemic exposure of ixazomib.

Strong CYP1A2 Inhibitors
Co-administration of Ninlaro with strong CYP1A2 inhibitors did not result in a clinically meaningful change in the systemic exposure of ixazomib based on a population PK analysis.

Effect of Ninlaro on Other Drugs
Ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immune-reactive protein levels. Ninlaro is not expected to produce drug-drug interactions via CYP inhibition or induction.

Transporter-Based Interactions
Ixazomib is a low affinity substrate of P-gp. Ixazomib is not a substrate of BCRP, MRP2 or hepatic OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Ninlaro is not expected to cause transporter-mediated drug-drug interactions.

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.

9. USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, Ninlaro can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology]. There are no human data available regarding the potential effect of Ninlaro on pregnancy or development of the embryo or fetus. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher then those observed in patients receiving the recommended dose *[see Data].* Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with Ninlaro.

9.2 Lactation

Risk Summary

No data are available regarding the presence of Ninlaro or its metabolites in human milk. The effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because the potential for serious adverse reactions from Ninlaro in breastfed infants is unknown, advise nursing women not to breastfeed during treatment with Ninlaro and for 90 days after the last dose.

9.3 Females and Males of Reproductive Potential

Contraception

Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because Ninlaro is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Advise women using hormonal contraceptives to also use a barrier method of contraception.

9.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

9.5 Geriatric Use
Of the total number of subjects in clinical studies of Ninlaro, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

9.6 Hepatic Impairment
In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of Ninlaro in patients with moderate or severe hepatic impairment [*see Dosage and Administration, Clinical Pharmacology*].

9.7 Renal Impairment
In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of Ninlaro in patients with severe renal impairment or ESRD requiring dialysis. Ninlaro is not dialyzable and therefore can be administered without regard to the timing of dialysis [*see Dosage and Administration, Clinical Pharmacology*].

10. ADVERSE EFFECTS/UNDESIRABLE EFFECTS

As ixazomib 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 safety profile of NINLARO is based on available clinical trial data and post-marketing experience to 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%), back pain (25% vs. 21%), rash (25% vs. 15%), peripheral oedema (24% vs. 19%), vomiting (23% vs. 12%) and bronchitis (20% vs. 15%). Serious adverse reactions reported in ≥ 2% of patients included diarrhoea (3%), 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 decreasing seriousness.

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 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 patients in the ixazomib regimen and 1% of patients in the placebo regimen.

Rash

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

Peripheral neuropathy

Peripheral neuropathy occurred in 28% of patients in the ixazomib regimen compared to 22% of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported in 2% of patients in the ixazomib regimen compared to 1% in the placebo regimen. The most commonly reported reaction was peripheral sensory neuropathy (21% and 15% in the ixazomib and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 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 5% in the placebo regimen), dry eye (6% in the ixazomib regimen and 1% in the placebo regimen), conjunctivitis (8% in the ixazomib regimen and 2% in the placebo regimen) and cataract (13% in the ixazomib regimen and 17% in the placebo regimen). Grade 3 adverse reactions were reported in 6% of patients 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%), 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.

[†] Standardised MedDRA Queries (SMQs)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

11. OVERDOSE AND TREATMENT

Overdose has been reported in patients taking Ninlaro. Symptoms of overdose are generally consistent with the known risks of Ninlaro (see ADVERSE EFFECTS/UNDESIRABLE EFFECTS). 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 Ninlaro overdose. In the event of an overdose, monitor the patient closely for adverse reactions and provide appropriate supportive care. Ixazomib is not dialyzable (see Pharmacokinetics).

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

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixazomib is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib induced apoptosis of multiple myeloma cell lines 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 antitumor activity in a mouse multiple myeloma tumor xenograft model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Ninlaro did not prolong the QTc interval at clinically relevant exposures based on pharmacokinetic-pharmacodynamic analysis of data from 245 patients.

12.3 CLINICAL STUDIES

TOURMALINE-MM1

The efficacy and safety of Ninlaro in combination with lenalidomide and dexamethasone was evaluated in a randomized, double-blind, placebo-controlled, multicenter study in patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy.

Patients who were refractory to lenalidomide or proteasome inhibitors were excluded from the study.

A total of 722 patients were randomized in a 1:1 ratio to receive either the combination of Ninlaro, lenalidomide and dexamethasone (N=360; Ninlaro regimen) or the combination of placebo, lenalidomide and dexamethasone (N=362; placebo regimen) until disease progression or unacceptable toxicity. Randomization was stratified according to number of prior lines of therapy (1 versus 2 or 3), myeloma International Staging System (ISS) (stage I or II versus III), and previous therapy with a proteasome inhibitor (exposed or naïve). Twenty three percent (N=166) of the patients had light chain disease and 12% (N=87) of patients had free light chain-measurable only disease.

Thromboprophylaxis was recommended for all patients in both treatment groups according to the lenalidomide prescribing information. Antiemetics were used in 19% of patients in the Ninlaro regimen and 12% of patients in the placebo regimen; antivirals in 64% and 60%, respectively, and antihistamines in 27% and 19%, respectively. These 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 prescribing information. Treatment continued until disease progression or unacceptable toxicities.

Table 6 summarizes the baseline patient and disease characteristics in the study. The baseline demographics and disease characteristics were balanced and comparable between the study regimens.

Table 6: Baseline Patient and Disease Characteristics.

	Ninlaro + Lenalidomide and Dexamethasone (N=360)	**Placebo + Lenalidomide and Dexamethasone (N=362)**
Patient Characteristics		
Median age in years (range)	66 (38, 91)	66 (30, 89)
Gender (%) Male/ Female	58/42	56/44
Age Group (%[<65/ ≥65 years])	41/59	43/57
Race n (%)		
White	310 (86)	301 (83)
Black	7 (2)	6 (2)
Asian	30 (8)	34 (9)
Other or Not Specified	13 (4)	21 (6)
ECOG performance status, n (%)		
0 or 1	336 (93)	334 (92)
2	18 (5)	24 (7)
Missing	6 (2)	4 (1)
Creatinine clearance, n (%)		
<30 mL/min	5 (1)	5 (1)
30-59 mL/min	74 (21)	95 (26)
≥60mL/min	281 (78)	261 (72)
Disease Characteristics		
Myeloma ISS stage, n (%)		
Stage I or II	315 (87)	320 (88)
Stage III	45 (13)	42 (12)
Prior line therapies n (%)		
Median (range)	1 (1, 3)	1 (1, 3)
1	224 (62)	217 (60)
2 or 3	136 (38)	145 (40)
Status at Baseline n (%)		
Relapsed	276 (77)	280 (77)
Refractory*	42 (12)	40 (11)
Relapsed and Refractory	41 (11)	42 (12)
Type of Prior Therapy n (%)		
Bortezomib containing	248 (69)	250 (69)
Carfilzomib containing	1 (<1)	4 (1)
Thalidomide containing	157 (44)	170 (47)
Lenalidomide containing	44 (12)	44 (12)
Melphalan containing	293 (81)	291 (80)
Stem cell transplantation	212 (59)	199 (55)
High risk (deletion (del) 17, t(4:14) and/ or t(14:16)	75 (21)	62 (17)
deletion del (17)	36 (10)	33 (9)

*Primary refractory, defined as best response of stable disease or disease progression on all prior lines of therapy, was documented in 7% and 6% of patients in the Ninlaro regimen and placebo regimens, respectively.

The efficacy of Ninlaro was evaluated by progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria as assessed by a blinded independent review committee (IRC) based on central lab results. Response was assessed every four weeks until disease progression.
The approval of Ninlaro was based upon a statistically significant improvement in PFS of the Ninlaro regimen compared to the placebo regimen. PFS results are summarized in Table 7 and shown in Figure 1.

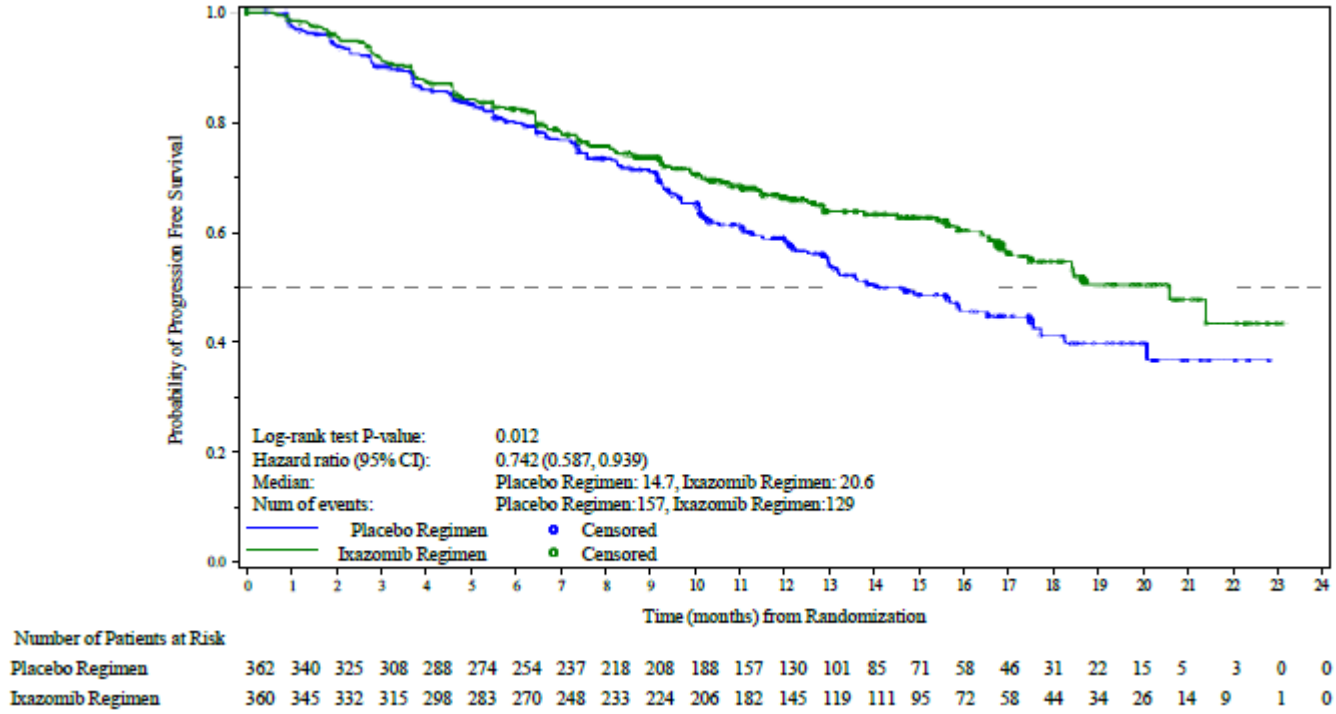
Table 7: Progression-Free Survival and Response Rate

	Ninlaro + Lenalidomide and Dexamethasone (N=360)	**Placebo + Lenalidomide and Dexamethasone (N=362)**
Progression-free Survival		
PFS Events, n (%)	129 (36)	157 (43)
Median (months) (95% CI)	20.6 (17.0, NE)	14.7 (12.9, 17.6)
Hazard Ratio* (95% CI)	0.74 (0.59, 0.94)	
p-value+	0.012	
Response Rate		
Overall Response Rate, n (%)	282 (78)	259 (72)
Complete Response	42 (12)	24 (7)
Very Good Partial Response	131 (36)	117 (32)
Partial Response	109 (30)	118 (33)

NE: Not evaluable.
*Hazard ratio is based on a stratified Cox's proportional hazard regression model. A hazard ratio less than 1 indicates an advantage for the Ninlaro regimen.
+P-value is based on the stratified log-rank test.

The median time to response was 1.1 months in the Ninlaro regimen and 1.9 months in the placebo regimen. The median duration of response was 20.5 months in the Ninlaro regimen and 15 months in the placebo regimen for responders in the response evaluable population.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival



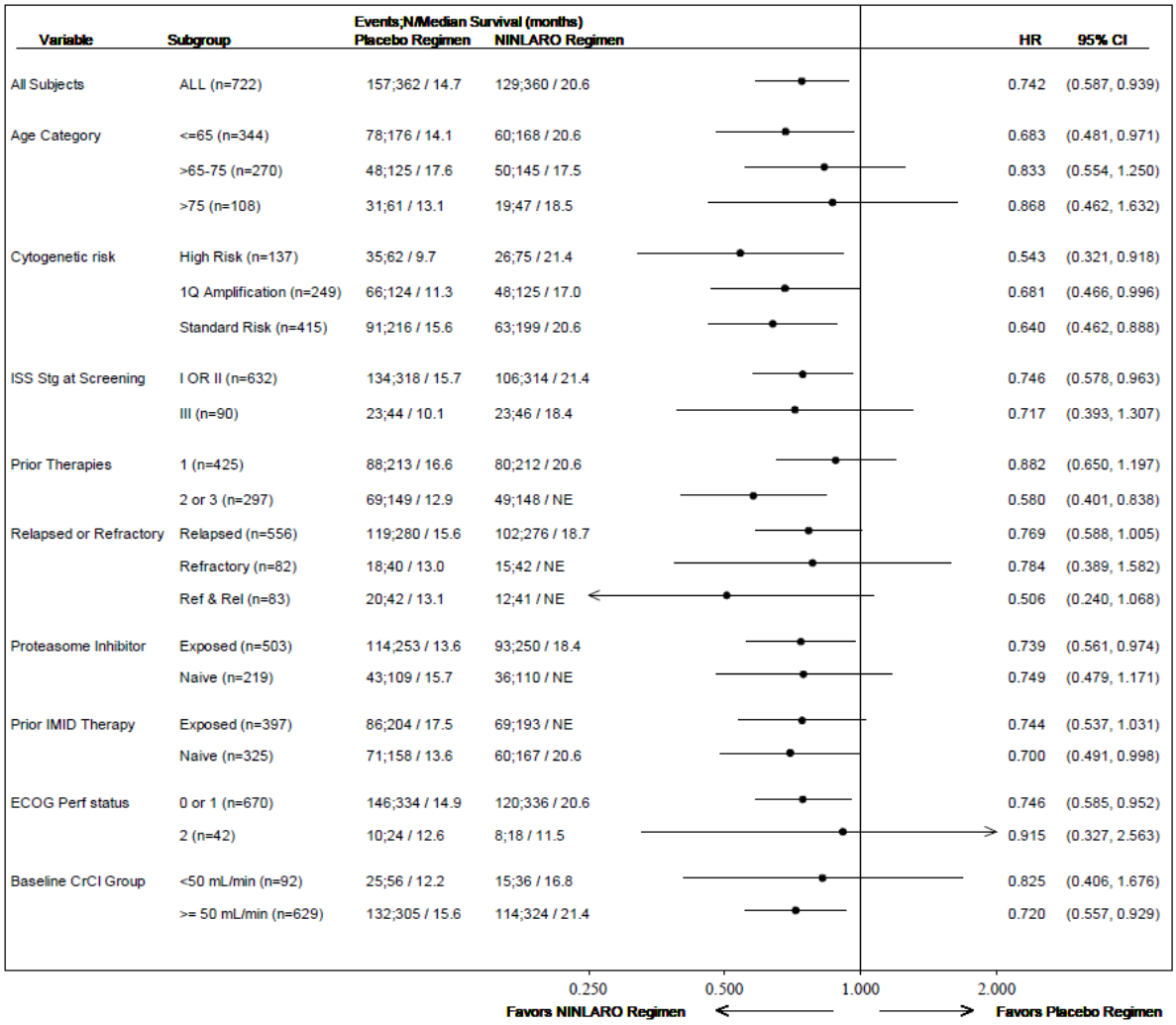
A second, non-inferential, PFS analysis was conducted with a median follow up of 23 months. At this analysis, estimated median PFS was 20 months in the ixazomib regimen and 15.9 months in the placebo regimen (HR=0.82 [95% CI (0.67, 1.0)]) in the ITT population. For patients with one prior therapy, the median PFS was 18.7 months in the ixazomib regimen and 17.6 months in the placebo regimen (HR = 0.99). For patients with 2 or 3 prior therapies, PFS was 22.0 months in the ixazomib regimen and 13.0 months in the placebo regimen (HR = 0.62).

At the final analysis for OS at a median duration of follow up of approximately 85 months, median OS in the ITT population was 53.6 months for patients in the ixazomib regimen and 51.6 months for patients in the placebo regimen (HR = 0.94 [95% CI: 0.78, 1.13; p=0.495]). For patients with one prior therapy, the median OS was 54.3 months in the ixazomib regimen and 58.3 months in the placebo regimen (HR = 1.02 [95% CI: 0.80, 1.29]). For patients with 2 or 3 prior therapies, the median OS was 53.0 months in the ixazomib regimen and 43.0 months in the placebo regimen (HR = 0.85 [95% CI: 0.64, 1.11]).

A randomised, double blind, placebo controlled Phase 3 study was conducted in China (N=115) with a similar study design and eligibility criteria. Many of the patients enrolled in the study had advanced disease with Durie Salmon Stage III (69%) at initial diagnosis and a treatment history of receiving at least 2 prior therapies (60%) and being thalidomide refractory (63%). At the primary analysis (median follow up of 8 months and a median of 6 cycles), the median PFS was 6.7 months in the ixazomib regimen compared to 4 months in the placebo regimen (p value=0.035, HR=0.60). At the final analysis for OS at a median follow up of 19.8 months, OS was improved for patients treated in the ixazomib regimen compared with placebo [p value=0.0014, HR=0.42, 95% CI: 0.242, 0.726]).

As multiple myeloma is a heterogeneous disease, benefit may vary across subgroups in the Phase 3 study (C16010) (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 ixazomib regimen, one patient had a confirmed partial response and 3 confirmed stable disease (however 2 were unconfirmed partial response and 1 was an unconfirmed very good partial response). Of the 5 patients in the placebo regimen, 2 had a confirmed very good partial response.

Quality of life as assessed by global health scores (EORTC QLQ-C30 and MY-20) was maintained during treatment and was similar in both treatment regimens in the Phase 3 study (C16010).

12.3 Pharmacokinetics

Absorption

After oral administration, the median time to achieve peak ixazomib plasma concentrations was one hour. The mean absolute oral bioavailability was 58%, based on population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 to 10.6 mg.

A food effect study conducted in patients with a single 4 mg dose of ixazomib showed that a high-fat meal decreased ixazomib AUC by 28% and C_{max} by 69% [*see Dosage and Administration*].

Distribution

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

Metabolism
After oral administration of a radiolabeled dose, ixazomib represented 70% of total drug-related material in plasma. 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 showed that no specific CYP isozyme predominantly contributes to ixazomib metabolism. At higher than clinical concentrations, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (< 1%).

Elimination
Based on a population PK analysis, systemic clearance was approximately 1.9 L/hr with inter-individual variability of 44%. The terminal half-life (t1/2) of ixazomib was 9.5 days. Following weekly oral dosing, the accumulation ratio was determined to be 2-fold.

Excretion
After administration of a single oral dose of ^{14}C-ixazomib to 5 patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in the feces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

Special Populations
Age, Sex, Race
There was no clinically meaningful effect of age (range 23-91 years), sex, body surface area (range 1.2-2.7 m^2), or race on the clearance of ixazomib based on population PK analysis.

Hepatic Impairment
The PK of ixazomib was 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 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). Dose-normalized mean AUC was 20% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function [*see Dosage and Administration*].

Renal Impairment
The PK of ixazomib was similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on 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). Mean AUC was 39% higher in patients with severe renal impairment or ESRD requiring dialysis as compared to patients with normal renal function. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not dialyzable [*see Dosage and Administration*].

Drug Interactions
Effect of Other Drugs on Ninlaro
Strong CYP3A Inducers
Co-administration of Ninlaro with rifampin decreased ixazomib C_{max} by 54% and AUC by 74% [*see Drug Interactions*].
Strong CYP3A Inhibitors

Co-administration of Ninlaro with clarithromycin did not result in a clinically meaningful change in the systemic exposure of ixazomib.

Strong CYP1A2 Inhibitors
Co-administration of Ninlaro with strong CYP1A2 inhibitors did not result in a clinically meaningful change in the systemic exposure of ixazomib based on a population PK analysis.

Effect of Ninlaro on Other Drugs
Ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immune-reactive protein levels. Ninlaro is not expected to produce drug-drug interactions via CYP inhibition or induction.

Transporter-Based Interactions
Ixazomib is a low affinity substrate of P-gp. Ixazomib is not a substrate of BCRP, MRP2 or hepatic OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Ninlaro is not expected to cause transporter-mediated drug-drug interactions.

13. NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay). Ixazomib was considered positive in an in vitro clastogenicity test in human peripheral blood lymphocytes. However, in vivo, ixazomib was not clastogenic in a bone marrow micronucleus assay in mice and was negative in an in vivo comet assay in mice, as assessed in the stomach and liver. No carcinogenicity studies have been performed with ixazomib.
Developmental toxicity studies in rats and rabbits did not show direct embryo-fetal toxicity below maternally toxic doses of ixazomib. 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.

14. STORAGE CONDITIONS

Do not store above 30°C. Do not freeze.
Store capsules in original packaging until immediately prior to use.
Shelf life
3 years.

15. PACKAGING AVAILABLE

Ninlaro capsule are available in 1 capsule in a single individually packaged PVC-Aluminum/Aluminum blister pack of 1 and 3 single packs in a carton. Not all are marketed.

16. HANDLING AND DISPOSAL

Ninlaro is a cytotoxic drug. Follow applicable special handling and disposal procedures. Do not open or crush capsules. Avoid direct contact with the capsule contents. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
Any unused medicinal product or waste material should be disposed in accordance with local requirements.

17. NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER

Manufacturer
Haupt Pharma Amareg GmbH
Donaustaufer Strasse 378
93055 Regensburg
Germany for
Takeda Pharmaceutical Company Ltd.

Product Registration Holder
Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B, Plaza 33,
No. 1, Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya, Selangor, Malaysia.

18. REVISION OF TEXT

Version: 2
Reference: USPI/EU SmPC/ CCDS v5
Last revision date: 1st March 2022