Report on the Deliberation Results

March 10, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour, and Welfare

Brand Name	Ninlaro Capsules 2.3 mg
	Ninlaro Capsules 3 mg
	Ninlaro Capsules 4 mg
Non-proprietary Name	Ixazomib Citrate (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	July 4, 2016

Results of Deliberation

In its meeting held on March 3, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as poisonous drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey should be continued until data are gathered from a certain number of patients so that the characteristics of users of the product are clearly identified and safety and efficacy data are promptly collected. The applicant should then take necessary measures to further ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

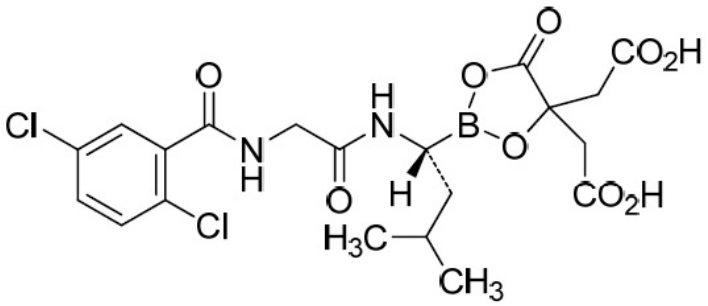
Review Report

February 21, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ninlaro Capsules 2.3 mg Ninlaro Capsules 3 mg Ninlaro Capsules 4 mg
Non-proprietary Name	Ixazomib Citrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	July 4, 2016
Dosage Form/Strength	Capsules: Each capsule contains 3.29 mg, 4.30 mg, or 5.73 mg of Ixazomib Citrate (equivalent to 2.3 mg, 3.0 mg, or 4.0 mg of ixazomib).
Application Classification	Prescription drug (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{20}H_{23}BCl_2N_2O_9$
Molecular weight: 517.12
Chemical name:
2,2'-{2-[(1*R*)-1-({[(2,5-Dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid

Items Warranting Special Mention

Orphan drug (Drug Designation No. 375 of 2016 [*28 yaku*], PSEHB/PED Notification No. 0225-1, of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 25, 2016)

Reviewing Office of New Drug V

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Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with relapsed or refractory multiple myeloma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of thrombocytopenia, gastrointestinal disorder, peripheral nerve disorder, skin disorder, infection, and posterior reversible encephalopathy syndrome need to be further investigated via post-marketing surveillance.

Indication
Relapsed or refractory multiple myeloma

Dosage and Administration
In combination with lenalidomide and dexamethasone, the usual adult dosage is 4 mg of ixazomib administered orally under fasting condition once weekly for 3 weeks (Days 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient's condition.

Conditions of Approval
1. The applicant is required to develop and appropriately implement a risk management plan.

2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey should be continued until data are gathered from a certain number of patients so that the characteristics of users of the product are clearly identified and safety and efficacy data are promptly collected. The applicant should then take necessary measures to further ensure proper use of the product.

Attachment

Review Report (1)

January 10, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Ninlaro Capsules 2.3 mg Ninlaro Capsules 3 mg Ninlaro Capsules 4 mg
Non-proprietary Name	Ixazomib Citrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	July 4, 2016
Dosage Form/Strength	Capsules: Each capsule contains 3.29 mg, 4.30 mg, or 5.73 mg of Ixazomib Citrate (equivalent to 2.3 mg, 3.0 mg, or 4.0 mg of ixazomib).
Proposed Indication	Relapsed or refractory multiple myeloma
Proposed Dosage and Administration	In combination with other antineoplastic drugs, the usual adult dosage is 4 mg of ixazomib administered orally under fasting condition once weekly for 3 weeks (Day 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient's condition.

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List of Abbreviations

ΔΔQTcF	change from baseline in QTcF
ΔΔQTcP	change from baseline in QTcP
^{14}C-ixazomib	^{14}C-labeled ixazomib
AGP	α1-acid glycoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
application	application for marketing approval
AST	aspartate aminotransferase
ATF3	activating transcription factor 3
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die

BiP	binding immunoglobulin protein
BSA	body surface area
BUN	blood urea nitrogen
CHOP	CCAAT-enhancer-binding protein homologous protein
CI	confidence interval
CL_r	renal clearance
CrCL	creatinine clearance
CYP	cytochrome P450
DEREK	Deductive Estimation of Risk from Existing Knowledge
DEX	dexamethasone
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DN	dose normalized
ECOG	Eastern Cooperative Oncology Group
efflux ratio	Ratio of permeability coefficient in the direction of secretion to that in the direction of absorption
eIF2α	eukaryotic translation initiation factor 2A
GADD34	growth arrest and DNA damage-inducible protein 34
HDT-ASCT	high-dose chemotherapy with autologous hematopoietic stem cell transplantation
hERG	human *ether-a-go-go* related gene
HLT	high level term
HPLC	high performance liquid chromatography
HP-β-CD	hydroxypropyl-β-cyclodextrin
HSA	human serum albumin
HUVEC	human umbilical vascular endothelial cell
Ig	immunoglobulin
IMWG	International Myeloma Working Group
IMWG criteria	evaluation criteria established by International Myeloma Working Group
IR	infrared spectroscopy
IRC	independent review committee
ISS	international staging system
ITT	intent-to-treat
ixazomib	ixazomib citrate
ixazomib/Ld	concomitant use of ixazomib with Ld regimen
Ki	inhibition constant
LC-MS/MS	liquid chromatography/tandem mass spectrometry
Ld regimen	concomitant use of lenalidomide with DEX (oral lenalidomide 25 mg administered from Day 1 to Day 21 and oral DEX 40 mg on Days 1, 8, 15, and 22 in each treatment cycle of 28 days)
lenalidomide	lenalidomide hydrate
MATE	multidrug and toxin extrusion
M-CSF	macrophage colony-stimulating factor
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MSC	mesenchymal stem cell
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN	National Comprehensive Cancer Network
NCCN Guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query Multiple Myeloma and Other Plasma Cell Neoplasms

NE	not evaluable
NMR	nuclear magnetic resonance spectrum
NOD-SCID mouse	non-obese diabetic severe combined immunodeficient mouse
NOXA	phorbol-12-myristate-13-acetate-induced protein 1
NTCP	sodium taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
old testing method	method for dissolution test used during the early stage of development
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PARP	poly (ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
placebo/Ld	concomitant use of placebo with Ld regimen
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
proposed testing method	dissolution test method established for specifications, which detects difference in dissolution behavior between drug products with a higher sensitivity than that achieved by the old testing method
PT	preferred term
PUMA	p53 upregulated modulator of apoptosis
QD	quaque die
QOL	quality of life
QTcF	QT interval corrected by Fridericia's method
QTcP	QT interval corrected by population-based correction method
RANKL	receptor activator of NF-κB ligand
SCID mouse	severe combined immunodeficient mouse
SMQ	standard MedDRA queries
SOC	system organ class
TRAP	tartrate-resistant acid phosphatase
UV/VIS	ultraviolet-visible spectrum
V4	volume of the second peripheral compartment
WM	Waldenström's macroglobulinemia

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Overview of the product submitted for registration

Ixazomib citrate (hereinafter referred to as ixazomib) is a proteasome inhibitor discovered by Millennium Pharmaceuticals, Inc. (the US). Ixazomib binds to the site with chymotrypsin-like activity (β5 subunit) in 20S proteasome, a component of the ubiquitin-proteasome system, thereby inhibiting the activity of 20S proteasome. The inhibition of 20S proteasome activity is expected to induce tumor cell apoptosis, resulting in tumor growth suppression.

1.2 Development history, etc.

A foreign Phase I study (Study C16001) of ixazomib monotherapy was started in March 2009 involving patients with advanced solid cancer by Millennium Pharmaceuticals, Inc. A Phase III study (Study C16010) on concomitant use of ixazomib with Ld regimen (ixazomib/Ld) therapy involving patients with relapsed or refractory multiple myeloma (MM) was also conducted from August 2012 by Millennium Pharmaceuticals, Inc.

In the US and EU, the applications for marketing approval of ixazomib were submitted in July 2015 with pivotal data based on Study C16010. Ixazomib was approved in the US in November 2015. Its indication was described as "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," In the EU, the product was approved in November 2016 with the description of indication "NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."

As of November 2016, ixazomib was approved in 6 countries and regions for the indication for MM.

In Japan, the applicant started a Phase I study (Study TB-MC010034) on ixazomib monotherapy or ixazomib/Ld therapy in June 2012 involving patients with relapsed or refractory MM. Also, patient enrollment in Study C16010 started from November 2013.

Recently, an application for marketing approval of ixazomib was submitted with the results of Study C16010 as the pivotal data.

Ixazomib was designated as an orphan drug with the expected indication of "relapsed or refractory multiple myeloma" in February 2016 (Drug Designation No. 375 of 2016 [*28 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to practically white powder. The general properties of the drug substance, including description, thermal analysis, particle size, hygroscopicity, solubility, equilibrium constant, acid dissociation constant, and distribution coefficient were determined. The drug substance is present in a total of 9 crystalline forms, 5 types of [redacted] and 4 types of [redacted], but it has been confirmed that, in the commercial-scale production, only [redacted], the thermodynamically most stable form, is formed, and that [redacted] does not change in stability studies.

The chemical structure of the drug substance was elucidated by elemental analysis, mass spectrometry, infrared spectroscopy (IR), ultraviolet-visible spectrum (UV/VIS), single crystal X-ray diffractometry, and nuclear magnetic resonance spectrum (NMR) (^{1}H-NMR and ^{13}C-NMR).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as the starting materials.

[redacted] of [redacted],[1] [redacted] of [redacted],[2] as well as [redacted] and [redacted] were defined as critical steps, and the in-process control parameters and the control values were established for [redacted], [redacted], [redacted], and [redacted] processes. [redacted] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and high performance liquid chromatography [HPLC]), purity (elemental impurities [inductively coupled plasma source mass spectrometry], related substances [HPLC], residual solvents [gas chromatography], enantiomer [HPLC], and [redacted]), water content, particle size, crystalline forms (X-ray powder diffraction method), and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows stability studies conducted on the drug substance. A photostability test showed that the drug substance is photostable.

Table 1. Stability studies of drug substance

Test	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	5 ± 3°C	-	Polyethylene container	36 months
Accelerated testing	3 commercial-scale batches	25 ± 2°C	60 ± 5%RH		6 months

Based on the above, a retest period of 36 months was proposed for the drug substance when stored at 5°C ± 3°C in polyethylene containers. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release hard capsules, each containing 3.29 mg, 4.30 mg, or 5.73 mg of the drug substance (2.3 mg, 3.0 mg, or 4.0 mg as ixazomib). The drug product contains microcrystalline cellulose, talc, and magnesium stearate as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] processes.

[redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] are identified as the critical steps, and in-process control parameters and control values are defined in [redacted] and [redacted] processes.

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (UV/VIS and HPLC), purity (related substances [HPLC]), water content, uniformity of dosage unit (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows the stability studies conducted on the drug product. A photostability test showed that the drug product is photostable.

1) [redacted]
2) [redacted]

Table 2. Stability studies of drug product

Content	Test	Primary batch	Temperature	Humidity	Storage form	Storage period
2.3 mg	Long-term testing	3 commercial-scale batches	30 ± 2°C	75 ± 5%RH	[redacted]	[redacted][*1]
		3 commercial-scale batches				12 months[*2]
	Accelerated testing	6 commercial-scale batches	40 ± 2°C			6 months[*3]
3 mg	Long-term testing	3 commercial-scale batches	30 ± 2°C			[redacted][*1]
		3 commercial-scale batches				12 months[*2]
	Accelerated testing	6 commercial-scale batches	40 ± 2°C			6 months[*3]
4 mg	Long-term testing	3 commercial-scale batches	30 ± 2°C			[redacted][*1]
		2 commercial-scale batches				12 months[*2]
		1 commercial-scale batch				6 months[*2]
	Accelerated testing	6 commercial-scale batches	40 ± 2°C			6 months[*3]

[*1] Dissolution was tested (a) by Testing Method A from the start through Month [redacted] of the test, (b) by Testing Method B in Month [redacted], and (c) by Testing Methods A and B in Month [redacted] (2 of 3 batches) and Month [redacted] (1 of 3 batches). [*2] Dissolution was tested by Testing Method B. [*3] Dissolution was tested by Testing Method A on 3 of 6 batches and by Testing Method B on the other 3 batches.

Based on the above, the shelf life of 36 months was been proposed for the drug product when blister-packaged with [redacted] and stored at room temperature. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.R.1 Determination of shelf life

Stability data of the drug product up to 36 months tested by Testing Method B[3)] are not available. Therefore, PMDA asked the applicant to explain the appropriateness of the 36-month shelf life of the drug product.

The applicant's explanation:
The following observations justify the drug product's shelf life to be 36 months:

- In both Testing Methods B and A,[4)] approximately [redacted]% of ixazomib was dissolved in [redacted] minutes. It is thus possible to evaluate the stability of the drug product by referring to the results of obtained by Testing Method A.
- Testing Method A did not show over-time change in the dissolution up to [redacted] months in the long-term testing, demonstrating the stability of the drug product.
- Testing Method B produced the following stability data:
  - ➢ No over-time change occurred in the dissolution over [redacted] months in the long-term testing and over 6 months in the accelerated testing, meeting the specifications.
  - ➢ No over-time change occurred in the dissolution from Month [redacted] to [redacted] in the long-term testing, meeting the specifications.

PMDA accepted the applicant's explanation.

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3) Testing Method: [redacted], volume of test medium, [redacted] mL; rotation speed, [redacted] rpm; specification limit, ≥[redacted]% in [redacted] minutes

4) Testing Method: [redacted], volume of test medium, [redacted] mL; rotation speed, [redacted] rpm for [redacted] minutes followed by [redacted] rpm for [redacted] minutes; specification limit, mean of [redacted] minutes was reported.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, the dose and the concentration of ixazomib citrate are expressed in terms of ixazomib.

3.1 Primary pharmacodynamics

3.1.1 Binding to proteasome (CTD 4.2.1.1-1)

The binding capacities of ixazomib and bortezomib to chymotrypsin-like activity site (β5 subunit) of purified human 20S proteasome were investigated using a specific chemiluminescent substrate. Table 3 shows the results.

Table 3. Binding of ixazomib and bortezomib to β5 subunit of 20S proteasome

	Ixazomib	Bortezomib
Binding rate constant ($\times 10^3$ sec^{-1} $[mol/L]^{-1}$)	700 [450, 940]	195 [140, 250]
Dissociation rate constant ($\times 10^{-3}$ sec^{-1})	0.66 [0.19, 1.1]	0.11 [0.067, 0.15]
Dissociation half-life (min)	18 [6.8, 30]	110 [71, 150]

n = 3, arithmetic mean [95% CI]

3.1.2 Inhibition of proteasome

3.1.2.1 *In vitro* (CTD 4.2.1.1-1, 4.2.1.1-2)

The inhibitory effects of ixazomib and bortezomib against caspase-like activity, trypsin-like activity, and chymotrypsin-like activity of purified human 20S proteasome were investigated using chemiluminescent substrates specific to each activities. Table 4 shows the results.

Table 4. Inhibitory effects of ixazomib and bortezomib against caspase-like activity, trypsin-like activity, and chymotrypsin-like activity of purified 20S proteasome

	Ixazomib		Bortezomib	
	n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
Caspase-like activity	1	31	12	24 [14.5, 40]
Trypsin-like activity	1	3500	1	1200
Chymotrypsin-like activity	3	3.4 [2.8, 4.1]	45	2.4 [2.0, 2.9]

Geometric mean [95% CI] (individual value for n = 1)

The inhibitory effects of ixazomib and bortezomib against chymotrypsin-like activity of purified human 20S proteasome and purified murine 20S immunoproteasome were investigated using a chemiluminescent substrate specific to chymotrypsin-like activity. Table 5 shows the results.

Table 5. Inhibitory effects of ixazomib and bortezomib against chymotrypsin-like activity of 20S proteasome and 20S immunoproteasome

	Ixazomib		Bortezomib	
	n	Ki (nmol/L)	n	Ki (nmol/L)
20S proteasome	3	0.93 [0.64, 1.4]	3	0.55 [0.34, 0.89]
20S immunoproteasome	1	0.4	1	0.2

Geometric mean [95% CI] (individual value for n = 1)

The inhibitory effects of ixazomib and bortezomib against trypsin-like activity and chymotrypsin-like activity of 20S proteasome were investigated in human colorectal cancer-derived HCT-116 cell lines, using chemiluminescent substrates specific to each activity. Table 6 shows the results.

Table 6. Inhibitory effects of ixazomib and bortezomib against trypsin-like activity and chymotrypsin-like activity of 20S proteasome

	Ixazomib		Bortezomib	
	n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
Trypsin-like activity	4	9100 ± 18,000	6	410 ± 110
Chymotrypsin-like activity	6	7.5 ± 0.37	3	3.6 ± 0.21

Geometric mean ± SE

Human lung cancer-derived Calu-6 cell lines were treated with 1 μmol/L of ixazomib or bortezomib and, before and 4 hours after removal of ixazomib or bortezomib, chymotrypsin-like activity of 20S proteasome was investigated using a chemiluminescent substrate specific to chymotrypsin-like activity.

Table 7 shows the results.

Table 7. Chymotrypsin-like activity of 20S proteasome before and after removal of ixazomib or bortezomib

	Ixazomib		Bortezomib	
	n	Activity rate* (%)	n	Activity rate* (%)
Before drug removal	5	7.1 [3.6, 10.6]	5	3.5 [2.0, 4.9]
After drug removal	5	69 [66, 71]	5	20 [18, 23]

Arithmetic mean [95% CI]; * Activity rate = (activity before or after drug removal) / (activity before drug treatment) × 100

Using human breast cancer-derived MDA-MB-231 cell lines expressing polyubiquitinated luciferase, the inhibitory effects of ixazomib and bortezomib against 20S proteasome activity were investigated on a basis of luciferase activity. EC_{50} (geometric mean [95% confidence interval (CI)], n = 4 and 29, respectively) of ixazomib and bortezomib was 525 [330, 840] and 310 [230, 400] nmol/L, respectively.

Using human fetal kidney-derived HEK293 cell lines expressing luciferase in NF-κB-dependent manner, the inhibitory effects of ixazomib and bortezomib against 20S proteasome activity were investigated on a basis of luciferase activity. IC_{50} (geometric mean [95% CI], n = 7 and 23, respectively) of ixazomib and bortezomib was 55 [33, 91] and 33 [27, 40] nmol/L, respectively.

3.1.2.2 *In vivo* (CTD 4.2.1.1-9)

Severe combined immunodeficient (SCID) mice (n = 3/group) subcutaneously transplanted with human MM-derived MM.1S cell lines received a single intravenous dose of ixazomib (2.0 mg/kg) or a single oral dose of ixazomib (6.0 mg/kg). The inhibitory effect of ixazomib against chymotrypsin-like activity of 20S proteasome in the tumor tissue was investigated using a chemiluminescent substrate specific to chymotrypsin-like activity. Chymotrypsin-like activity in 20S proteasome decreased in the ixazomib group as compared with the control (5% hydroxypropyl-β-cyclodextrin [HP-β-CD]) group.

3.1.3 Apoptosis induction

3.1.3.1 *In vitro* (CTD 4.2.1.1-5)

Using human MM-derived NCI-H929 and MM.1S cell lines, apoptosis induction effect of ixazomib was investigated by Western blotting base on the expression levels of truncated form of caspase 3, 8, and 9 and truncated form of poly (ADP-ribose) polymerase (PARP). The results demonstrated an apoptosis induction effect of ixazomib.

Using MM.1S cell lines, the effect of ixazomib on p53 signaling pathway, a pathway which is known to be involved in apoptosis induction, was investigated by Western blotting based on the expression levels of p53, p21, phorbol-12-myristate-13-acetate-induced protein 1 (NOXA), and p53 upregulated modulator of apoptosis (PUMA). The results showed p53 signaling pathway activated by ixazomib.

Using MM.1S cell lines, the effect of ixazomib on unfolded protein response, which is known to be involved in apoptosis induction, was investigated by Western blotting based on the expression levels of binding immunoglobulin protein (BiP), phosphorylated eukaryotic translation initiation factor 2A (eIF2α), and CCAAT-enhancer-binding protein homologous protein (CHOP). The results showed unfolded protein response activated by ixazomib.

3.1.3.2 *In vivo* (CTD 4.2.1.1-9)

SCID mice (n = 3/group) subcutaneously transplanted with MM.1S cell lines received a single intravenous dose of ixazomib (2.0 mg/kg) or a single oral dose of ixazomib (6.0 mg/kg). Apoptosis induction effect of ixazomib was investigated based on the expression level of truncated form of caspase 3 in the tumor tissue, and unfolded protein response of ixazomib was investigated based on activating transcription factor 3 (ATF3) and growth arrest and DNA damage-inducible protein 34 (GADD34) in the tumor tissue. Results showed apoptosis induction and activation of unfolded protein response in the ixazomib group as compared with the control (5%HP-β-CD) group.

3.1.4 Inhibition of neovascularization (CTD 4.2.1.1-5)

Inhibitory effect of ixazomib against lumen formation in human umbilical vascular endothelial cell (HUVEC) was investigated by microscopic counting of branching points. Ixazomib caused a statistically significant inhibition of lumen formation as compared with the control (0.1% dimethyl sulfoxide [DMSO]) ($P < 0.001$, one-way ANOVA).

3.1.5 Effect on osteoclasts and osteoblasts (CTD 4.2.1.1-7)

Inhibitory effects of ixazomib and bortezomib against osteoclast differentiation were investigated. Human peripheral blood mononuclear cell (PBMC) was cultured in a medium containing macrophage colony-stimulating factor (M-CSF, 25 ng/mL) and receptor activator of NF-κB ligand (RANKL, 50 ng/mL) in the presence of ixazomib or bortezomib, and tartrate-resistant acid phosphatase (TRAP)-positive cells with ≥3 nuclei were counted. Both ixazomib and bortezomib caused a statistically significant inhibition of osteoclast differentiation as compared with the control (0.1% DMSO) ($P < 0.05$, Mann-Whitney U test).

Inhibitory effects of ixazomib and bortezomib against bone-resorbing activity of osteoclasts were investigated. Human PBMC was cultured in a medium containing M-CSF (25 ng/mL) and RANKL (50 ng/mL) on calcium phosphate-coated slides in the presence of ixazomib or bortezomib, and calcium absorption area was measured. Both ixazomib and bortezomib caused a statistically significant decrease of bone-resorbing activity of osteoclasts as compared with the control (0.1%DMSO) ($P < 0.05$, Mann-Whitney U test).

Enhancing effects of ixazomib and bortezomib on osteoblast differentiation were investigated. MM patient-derived primary culture mesenchymal stem cell (MSC) was cultured in a medium containing β-glycerophosphate (5 mmol/L), ascorbic acid (50 μg/mL), and dexamethasone (DEX, 80 nmol/L) in the presence of ixazomib or bortezomib, and alkaline phosphatase (ALP) activity was measured. Both ixazomib and bortezomib brought about a statistically significant enhancement of osteoblast differentiation as compared with the control (0.1% DMSO) ($P < 0.05$, Mann-Whitney U test).

Enhancing effects of ixazomib and bortezomib on the substrate calcification activity of osteoblasts were investigated. MM patient-derived primary culture MSC was cultured in a medium containing β-glycerophosphate (5 mmol/L), ascorbic acid (50 μg/mL), and DEX (80 nmol/L) in the presence of ixazomib or bortezomib, and calcium deposition was measured. Both ixazomib and bortezomib brought about a statistically significant increase in substrate calcification activity as compared with the control (0.1% DMSO) ($P < 0.05$, Mann-Whitney U test).

3.1.6 Effect on malignant tumor-derived cell lines

3.1.6.1 *In vitro* (CTD 4.2.1.1-5, 4.2.1.1-6, 4.2.1.1-8)

Growth-inhibitory effect of ixazomib was investigated using human MM-derived MM.1S, ANBL-6, RPMI-8226, and NCI-H929 cell lines, based on the amount of viable cell-derived adenosine triphosphate (ATP). LD_{50} (geometric mean ± standard error [SE], n = 3-11) of ixazomib was 25.8 ± 36.0, 24.3 ± 7.2, 5.9 ± 1.7, and 14.9 ± 0.7 nmol/L, respectively.

Using human MM-derived MM.1S, MM.1R, RPMI-8226, OPM1, OPM2, NCI-H929, and INA-6 cell lines, growth-inhibitory effect of ixazomib was investigated based on the activity of viable cell-derived reductases. Ixazomib (25 nmol/L) inhibited the growth of MM.1S, MM.1R, RPMI-8226, NCI-H929, and INA-6 cell lines by ≥90%, and OPM1 and OPM2 cell lines by 40% to 50%.

Growth-inhibitory effect of ixazomib was investigated using primary culture MM cells derived from 6 patients with MM including those who had relapse after prior regimen with bortezomib, lenalidomide, DEX, etc., and PBMC derived from 6 healthy adults, based on the amount of viable cell-derived ATP. Ixazomib inhibited the growth of primary culture MM cells derived from MM patients, and the growth inhibitory effect was greater against MM cells than against healthy adult-derived PBMC.

Growth-inhibitory effect of ixazomib in the presence of bone marrow stromal cells was investigated using MM.1S cell lines based on ^{3}H-thymidine uptake. Ixazomib inhibited the cell growth in the presence of bone marrow stromal cells.

Growth inhibitory effect of combined ixazomib and lenalidomide was investigated using MM.1S, ANBL-6, RPMI-8226, and NCI-H929 cell lines, based on the amount of viable cell-derived ATP. The effect of the concomitant use was evaluated by isobolographic analysis and the nonlinear mixed-effects model. The concomitant use of ixazomib with lenalidomide brought about an additive effect (MM.1S and RPMI-8226 cell lines) or a synergistic effect (ANBL-6 and NCI-H929 cell lines).

3.1.6.2 *In vivo* (CTD 4.2.1.1-10, 4.2.1.1-11, 4.2.1.1-12, 4.2.1.1-13, 4.2.1.1-14)

Tumor growth-inhibitory effect of ixazomib was investigated in SCID mice (n = 5 or 8/group) subcutaneously transplanted with MM.1S cell lines. When the mean tumor volume reached approximately 100 to 350 mm^3, the animals were randomized to receive orally ixazomib (1, 2, 4, 6, 8, or 10 mg/kg) on Days 1, 5, 8, 12, and 15 after randomization, and tumor volume was calculated on Day 19. A statistically significant tumor growth inhibition was observed in the ixazomib 1, 4, 6, 8, and 10 mg/kg groups as compared with the control (5% HP-β-CD) group ($P < 0.005$ in the ixazomib 1 and 4 mg/kg groups, $P < 0.001$ in the ixazomib 6, 8, and 10 mg/kg groups, linear mixed-effects model) (Figure 1).

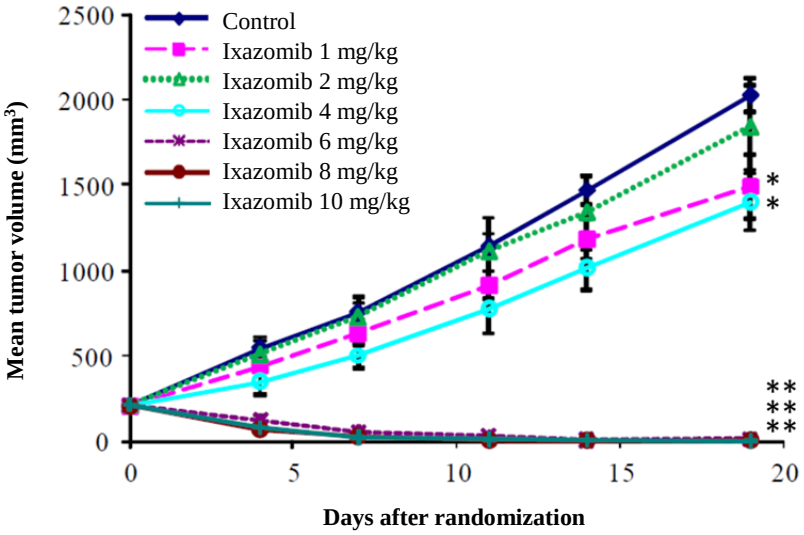

Figure 1. Tumor growth-inhibitory effect of ixazomib in mice
n = 5 or 8, arithmetic mean ± SE, * $P < 0.005$ against the control group
** $P < 0.001$ against the control group (linear mixed-effects model)

Tumor growth-inhibitory effect of ixazomib was investigated using SCID mice (n = 5 or 8/group) subcutaneously transplanted with MM.1S cell lines. When the mean tumor volume reached approximately 100 to 350 mm^3, the animals were randomized to receive intravenous ixazomib at 0.82, 1.64, 4.1, or 11.47 mg/kg on Day 0, 7, and 14 after randomization, or at 0.5, 1.0, 2.5, or 7.0 mg/kg on Day 0, 4, 7, 11, 14, and 17. Tumor volume was calculated on Day 19. A statistically significant tumor growth inhibition was observed in all ixazomib groups as compared with the control (5% HP-β-CD) group ($P < 0.05$ in the ixazomib 0.5 mg/kg group, $P < 0.001$ in all other groups, linear mixed-effects model).

Effects of ixazomib and bortezomib on survival, splenomegaly, and plasma immunoglobulin (Ig) G2a concentration were investigated using iMyc$^{C\alpha}$/Bcl-XL transgenic mice (n = 30/group) spontaneously developing plasma cell tumor. From 9 weeks of age, animals received intravenous ixazomib (18 mg/kg) or bortezomib (1.2 mg/kg) twice weekly for 6 weeks. As compared with the control (no treatment) group, both ixazomib and bortezomib groups showed a statistically significant prolongation of survival ($P < 0.0001$, Cox regression model), shrinkage of splenomegaly ($P < 0.05$, one-way ANOVA), and suppression of increase in plasma IgG2a concentration ($P < 0.05$, one-way ANOVA).

Effects of ixazomib and bortezomib to inhibit tumor growth and osteolytic lesion (separation of cranial sagittal suture) were investigated using non-obese diabetic severe combined immunodeficient (NOD-SCID) mice (n = 10/group) intravenously transplanted with mouse plasmacytoma-derived DP54 cell lines expressing luciferase. Starting from Day 6 after transplantation, mice received daily subcutaneous ixazomib 3 mg/kg quaque die (QD) for a total of 15 doses and intravenous ixazomib 11 mg/kg twice weekly for a total of 5 doses, or intravenous bortezomib 0.7 mg/kg twice weekly for a total of 5 doses. Mean photon flux densities (tumor volumes) were calculated on Day 20, and the areas of sagittal suture separation on Day 23. As compared with the control (5% HP-β-CD) group, all ixazomib and bortezomib groups showed a statistically significant inhibition of tumor growth ($P < 0.05$, t-test). Ixazomib 11 mg/kg showed a statistically significant decrease in the area of sagittal suture separation ($P < 0.05$, one-way ANOVA).

Tumor growth-inhibitory effect of ixazomib and bortezomib were investigated using athymic nude mice (nude mice) (n = 8/group) with DP54 cell lines expressing luciferase transplanted into cervical medullary cavity. Starting from Day 10 after transplantation, animals received intravenous ixazomib (13 mg/kg) or bortezomib (0.8 mg/kg) twice weekly for 3 weeks. Mean photon flux densities (tumor volumes) were calculated on Day 29. As compared with the control (5%HP-β-CD), both ixazomib and bortezomib statistically significantly inhibited tumor growth ($P < 0.05$, t-test).

3.2 Safety pharmacology

3.2.1 Effect on central nervous system

In repeated-dose toxicity studies in dogs, ixazomib-induced degeneration of nerve fibers, etc. was observed [see Sections “5.2.4 Three-month repeated oral dose toxicity study in dogs” and “5.2.5 Nine-month repeated oral dose toxicity study in dogs”].

3.2.2 Effect on cardiovascular system

3.2.2.1 Effect on hERG potassium current (CTD 4.2.1.3-1)

Effect of ixazomib on *ether-a-go-go* related gene (hERG) potassium current was investigated using HEK293 cell lines introduced with human hERG. IC_{50} of ixazomib was 59.6 μmol/L.

3.2.2.2 Effect on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3-2)

Dogs (n = 4) received successively 0.021, 0.14, and 0.21 mg/kg of oral ixazomib in a single dose, and its effect on blood pressure, heart rate, electrocardiogram (PR interval, QRS interval, QT interval, and QTc interval), and body temperature was investigated. Ixazomib did not affect any of these parameters.

3.2.3 Effect on respiratory system

In repeated-dose toxicity studies in rats and dogs, ixazomib did not affect the respiratory system [see Section “5.2 Repeated-dose toxicity”].

3.R Outline of the review conducted by PMDA

Based on the data submitted and the following reviews, PMDA concluded that ixazomib is expected to have efficacy in treatment of patients with MM.

3.R.1 Mechanism of action of ixazomib

The applicant’s explanation about the mechanism of action of ixazomib:
Ixazomib binds to the site with chymotrypsin-like activity in 20S proteasome (β5 subunit), a component of the ubiquitin-proteasome system, to inhibit the activity of 20S proteasome. This inhibitory action of Ixazomib is expected to induce apoptosis of tumor cells, leading to tumor growth suppression [see Sections “3.1.1 Binding to proteasome,” “3.1.2 Inhibition of proteasome,” “3.1.3 Apoptosis-inducing effect,” and “3.1.6 Effect on malignant tumor-derived cell lines”]. Ixazomib inhibited neovascularization and exhibited effects on osteoclasts and osteoblasts [see Sections “3.1.4 Inhibition of neovascularization” and “3.1.5 Effect on osteoclasts and osteoblasts”], but the relationship of these activities with the efficacy of ixazomib is unclear at present.

Bortezomib and carfilzomib are the approved drugs indicated for MM with proteasome-inhibitory activity similar to ixazomib. The applicant explained the differences in pharmacological characteristics, etc. between ixazomib and these 2 drugs as follows:

Ixazomib, bortezomib, and carfilzomib all mainly target the chymotrypsin-like activity site (β5 subunit) of 20S proteasome.

Despite different dissociation half-life from the chymotrypsin-like activity site between ixazomib and bortezomib, no clear difference was observed in either *in vitro* or *in vivo* effect of these drugs [see Sections "3.1.1 Binding to proteasome," "3.1.2 Inhibition of proteasome," and "3.1.6 Effect on malignant tumor-derived cell lines"]. Thus, the currently available information suggests that there is no clear difference in the pharmacological characteristics between ixazomib and bortezomib. However, in light of the observation that ixazomib inhibited the growth of primary MM cells derived from MM patients who had relapse after treatment with bortezomib [see Section "3.1.6 Effect on malignant tumor-derived cell lines"], ixazomib may be effective for MM that has become resistant to bortezomib. As for carfilzomib, it is unclear whether the pharmacological characteristic, etc. is different from that of ixazomib because there are no data of such comparison available at present.

PMDA's view:
The applicant's explanation is generally acceptable. However, available data do not adequately indicate the difference in the pharmacological characteristics, etc. between ixazomib and bortezomib and carfilzomib. Such information may help select patients suitable for the clinical use of ixazomib, and thus further collection of relevant data is recommended.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, the dose and the concentration of ixazomib citrate are expressed in terms of ixazomib, unless specified otherwise. The pharmacokinetics (PK) of ixazomib citrate and ixazomib was investigated in rats and dogs. Studies on plasma protein binding, drug-metabolizing enzymes, transporters of ixazomib citrate and ixazomib, etc. were conducted using biological samples derived from humans or animals.

4.1 Absorption

4.1.1 Single-dose studies

Male rats received a single intravenous dose of ixazomib (0.3 mg/kg) or a single oral dose of ixazomib (0.8 mg/kg) under fasting conditions. Male and female dogs received a single intravenous or oral dose of ixazomib (0.2 mg/kg) under fasting conditions. Male dogs received a single oral dose of ixazomib (0.145 mg/kg) under fasting conditions. Plasma ixazomib concentrations in these animals were measured (Table 8). No clear sex difference was observed in PK parameters of ixazomib in dogs. Bioavailability (BA) of oral ixazomib in male rats, male dogs, and female dogs was 41.1%, 75.3%, and 68.6%, respectively. The applicant explained that the differences in oral BA among the species were due to different hepatic clearance, etc., based on higher intrinsic clearance of ixazomib in rats than in dogs in *in vitro* studies [see Section "4.3.1 *In vitro*"].

Table 8. PK parameters of ixazomib in animals (single intravenous or oral dose)

Animal	Dose (route of administration)	Sex	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{24h} (ng·h/mL)	AUC_{48h} (ng·h/mL)	$t_{1/2}$ (h)
Rats	0.3 mg/kg (iv)	Male	4	167* ± 43.6	-	327 ± 79	-	32 ± 7.9
	0.8 mg/kg (po)	Male	6	59.1 ± 21.7	0.57 ± 0.36	358 ± 67.5	-	20 ± 9.4
Dogs	0.2 mg/kg (iv)	Female	3	924* ± 92.2	-	944 ± 118	1340 ± 170	-
		Male	3	946* ± 382	-	1120 ± 366	1820 ± 468	-
	0.2 mg/kg (po)	Female	3	237 ± 16.8	0.33 ± 0.14	598 ± 95.4	919 ± 171	-
		Male	3	233 ± 39.7	0.42 ± 0.14	890 ± 434	1370 ± 546	-
	0.145 mg/kg (po)	Male	4	279 ± 149	1.0 ± 0.7	973 ± 241	-	-

Arithmetic mean ± standard deviation (SD); * Plasma concentration at 5 min after administration; -, Not calculated

4.1.2 Repeated-dose studies

In each 28-day treatment cycle, male and female rats orally received ixazomib (0.2, 0.4, or 0.8 mg/kg QD) on Days 1, 8, and 15 under fed conditions, and plasma ixazomib concentrations were measured (Table 9). C_{max} and AUC_{24h} of ixazomib were almost linear within the dose range studied at all measuring time points. No clear sex difference was observed in PK parameters of ixazomib.

Table 9. PK parameters of ixazomib*1 (male and female rats, 6-month repeated oral doses)

Date of measurement (Day)	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{24h} (ng·h/mL)	
		Male	Female	Male	Female	Male	Female
1	0.2	3.68	5.12	1.0	0.5	75.4	89.6
	0.4	8.97	13.0	1.0	1.0	149	183
	0.8	21.4	66.4	1.0	0.5	282	496
15	0.2	7.04	7.83	1.0	1.0	148	134
	0.4	19.3	23.7	0.5	1.0	245	269
	0.8	51.2	51.9	1.0	1.0	431	421
43	0.2	6.35	9.98	1.0	0.5	123	127
	0.4	12.0	18.7	0.5	0.25	213	212
	0.8	30.5	69.7	0.5	0.25	334	305
169	0.2	5.42	6.55	0.5	4.0	98.2	116
	0.4	19.2	21.3	0.5	1.0	189	211
	0.8*2	62.1	44.7	0.5	1.0	252	288
183	0.2	8.70	10.9	0.5	0.25	142	132
	0.4	15.0	20.2	1.0	0.5	242	227
	0.8*2	27.7	32.8	0.25	0.5	287	317

*1 PK parameters were calculated based on the mean plasma ixazomib concentration (n = 3) at each measuring time point, *2 Because of lethal toxicity observed in female rats, the dose of ixazomib was reduced to 0.6 mg/kg from Day 57 in female rats.

In each 28-day treatment cycle, male and female dogs orally received ixazomib (0.05, 0.10, or 0.20 mg/kg QD) on Days 1, 8, and 15 under fed conditions, and plasma ixazomib concentrations were measured (Table 10). C_{max} and AUC_t of ixazomib were almost linear within the dose range studied at all measuring time points. No clear sex difference was observed in PK parameters of ixazomib.

Table 10. PK parameters of ixazomib (male and female dogs, 9-month repeated oral doses)

Date of measurement (Day)	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max} (h)		AUC_{24h} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
1	0.05	3	29.8 ± 9.05	48.0 ± 20.9	0.67 ± 0.29	0.50 ± 0	170 ± 10.3	267 ± 77.3
	0.10	6	107 ± 29.7	106 ± 55.7	0.67 ± 0.26	0.50 ± 0.27	466 ± 103	681 ± 173
	0.20	6	249 ± 79.5	305 ± 143	0.46 ± 0.10	0.50 ± 0	1400 ± 329	1410 ± 512
15	0.05	3	32.8 ± 9.05	39.6 ± 15.8	0.67 ± 0.29	0.75 ± 0.43	211 ± 4.37	192*
	0.10	6	101 ± 53.0	94.2 ± 48.0	0.50 ± 0.27	0.50 ± 0.27	519 ± 206	726 ± 315
	0.20	6	223 ± 80.5	211 ± 48.0	1.2 ± 1.4	0.50 ± 0.29	1250 ± 356	1530 ± 461
253	0.05	3	62.2 ± 39.7	52.1 ± 29.8	1.0 ± 0	1.0 ± 0	307 ± 106	311 ± 105
	0.10	6	134 ± 33.2	137 ± 74.7	0.83 ± 0.26	0.58 ± 0.20	694 ± 103	695 ± 242
	0.20	6	334 ± 78.9	332 ± 108	0.33 ± 0.13	0.54 ± 0.25	1350 ± 153	1770 ± 336
267	0.05	3	106 ± 49.9	61.0 ± 29.5	0.67 ± 0.29	0.83 ± 0.29	406 ± 84.5	415 ± 131
	0.10	6	165 ± 34.4	158 ± 40.3	0.58 ± 0.20	0.42 ± 0.13	956 ± 143	700 ± 222
	0.20	6	332 ± 76.7	375 ± 119	0.33 ± 0.13	0.38 ± 0.14	1640 ± 261	2090 ± 1040

Arithmetic mean ± SD; * n = 1 (individual value)

4.1.3 *In vitro* membrane permeability

Membrane permeability of ixazomib was investigated using human colon cancer-derived Caco-2 cell lines. Apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of ^{14}C-labeled ixazomib (^{14}C-ixazomib) (30 μmol/L[5)]) was 7.98×10^{-6} cm/sec in the presence of 10 μmol/L of GF120918 (inhibitor of P-glycoprotein [P-gp] and breast cancer resistance protein [BCRP]). $P_{app\ A\rightarrow B}$ of ^{3}H-atenolol (10 μmol/L) and ^{3}H-propranolol (10 μmol/L) was 0.617×10^{-6} and 27.6×10^{-6} cm/sec, respectively. The applicant explained that ixazomib has a moderate membrane permeability.

4.2 Distribution

4.2.1 Tissue distribution

Male pigmented rats received a single oral dose of ^{14}C-ixazomib (0.6 mg/kg[5)]), and male albino rats received a single intravenous dose of ^{14}C-ixazomib (0.3 mg/kg). Tissue radioactivity distribution in these animals was investigated by quantitative whole-body autoradiography. In pigmented rats, radioactivity was distributed in various tissues, reaching maximum concentrations in most tissues including blood within 4 hours post-dose. The maximum radioactivity concentrations in the urinary bladder, small intestine, liver, cecum, adrenals, renal cortex, large intestine, renal medulla, spleen, gastric mucosa, salivary gland, thyroid gland, pituitary gland, bone marrow, pancreas, heart, lymph nodes, esophagus, and brown fat were higher than in blood. Radioactivity concentrations in blood and in ocular uvea were similar between pigmented rats and albino rats. In both animal groups, radioactivity concentration in ocular uvea decreased with the decreased blood radioactivity concentration. The applicant explained that ixazomib and its metabolites have only a low affinity for melanin, based on the above results.

4.2.2 Plasma protein binding

^{14}C-ixazomib (0.05, 0.5, or 5 μg/mL) was added to plasma samples of mice, rats, dogs, and humans, and the mixtures were centrifuged for 15 minutes at room temperature. Plasma protein binding of ixazomib and its metabolites was investigated by ultrafiltration. The plasma protein binding rate of ixazomib and its metabolites was not concentration-dependent within the concentration range studied in either mice, rats, dogs, or human samples, with the rate being 82.7% to 86.3%, 86.7% to 89.9%, 81.9% to 83.3%, and 93.9% to 94.4%, respectively.

^{14}C-ixazomib (0.05, 0.5, or 5 μg/mL) was added to 4% human serum albumin (HSA) solution, 0.05% α1-acid glycoprotein (AGP) solution, or 4% HSA/0.05% AGP solution. The mixtures were centrifuged for 5 minutes[6)] at room temperature. Plasma protein binding of ixazomib and its metabolites was investigated by ultrafiltration. The plasma protein binding rate of ixazomib and its metabolites in 4% HSA solution, 0.05% AGP solution, and 4% HSA/0.05% AGP solution was 91.3% to 92.1%, 24.6% to 29.2%, and 91.1% to 92.2%, respectively, within the concentration range studied. The applicant explained that ixazomib and its metabolites bind mainly to serum albumin.

5) Dose or concentration of ixazomib

6) 1 minute for 0.05% AGP solution

4.2.3 Distribution in blood cells

Blood samples of mice, rats, dogs, and humans were incubated with ^{14}C-ixazomib (0.01, 0.1, or 1 μg/mL) at 37°C for 30 minutes, and distribution in blood cells of ixazomib and its metabolites was investigated. The distribution in blood cells of ixazomib and its metabolites was 92.0%, 91.3%, and 60.5%, respectively, in mice, 90.4%, 87.2%, and 45.6%, respectively, in rats, 91.6%, 91.1%, and 53.6%, respectively, in dogs, and 82.4%, 77.8%, and 42.8%, respectively, in humans, showing an ixazomib concentration-dependent decrease in the distribution in blood cells. The applicant explained that the concentration-dependent decrease in the distribution is likely to be caused by the saturation of the binding of ixazomib and its metabolites to proteasome in red blood cells.

Male rats and male dogs received a single oral dose of ^{14}C-ixazomib at 0.8[5)] or 0.15 mg/kg, respectively, and radioactivity concentration in blood and in plasma was measured. Radioactivity concentration in blood was higher than in plasma both in rats and dogs at all time points of measurement. The applicant explained that the results demonstrated the distribution of ixazomib and its metabolites in blood cells.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of ixazomib was not investigated. However, in a study of embryo-fetal development in rabbits, fetal toxicities such as variation of lumbar vertebral number and complete extra ribs were observed [see Section "5.5.3 Embryo-fetal development in rabbits"]. Based on these findings, the applicant explained that ixazomib and its metabolites may possibly pass through the placenta and be distributed in fetuses.

4.3 Metabolism

4.3.1 *In vitro*

Liver microsomes of male mice, male and female rats, male dogs, male monkeys, and humans were incubated with ^{14}C-ixazomib (50 μmol/L[5)]) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 20 minutes to investigate metabolites of ixazomib. In the samples of all animal species and humans, M1 (hemiaminal form) was detected as the main metabolite (the percentage relative to the total radioactivity in the sample was 15.1%, 19.7%, 6.7%, 16.9%, 18.2%, and 11.7%, respectively, in male mice, male rats, female rats, male dogs, male monkeys, and humans). Other metabolites detected were M2 (oxidative metabolite of M1), M3 (*N*-dealkylated form), M12 (amide hydrolysate), M20 (dichlorobenzamide), ML00790286 (dehydrogenated ixazomib), and UK-1 (structure unidentified).

Liver microsomes of mice, rats, dogs, monkeys, and humans were incubated with ixazomib (2 μmol/L) at 37°C for 30 minutes in the presence of NADPH, and intrinsic clearance of ixazomib was investigated. The intrinsic clearance in mice, rats, dogs, monkeys, and humans was 13.7, 5.52, 0.802, 2.98, and 0.917 L/h/kg, respectively.

Cytochrome P450 (CYP) isoforms involved in the metabolism of ixazomib in humans were investigated. Results were as shown below. The applicant explained that, in humans, ixazomib is metabolized mainly by pathways other than those mediated by CYP enzymes, judging from these results and from C_{max} of ixazomib (0.19 μmol/L, [see Section "6.2.1.1 Japanese Phase I study"]) at steady state following the administration of ixazomib at the proposed dosage regimen.

- [redacted] microsomes expressing CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) were incubated with ixazomib (0.1, 0.5, or 10 μmol/L) at 37°C for 15 minutes in the presence of NADPH, and the rate of the contribution of each CYP isoform to the metabolism of ixazomib was investigated. At ixazomib 10 μmol/L, the rate of the contribution of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 to ixazomib metabolism was 26.1%, 16.0%, 6.0%, <1%, 4.8%, 4.8%, and 42.3%, respectively. At ixazomib 0.1 and 0.5 μmol/L, the metabolic rate of ixazomib was similar between microsomes not expressing CYP and those expressing any of these CYP isoforms.

- Human liver microsomes were incubated with ^{14}C-ixazomib (10 μmol/L) at 37°C for 30 minutes in the presence of NADPH and an inhibitor of CYP isoform[7] (CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A), and contribution of each CYP isoform to ixazomib metabolism was investigated. Ixazomib metabolism was inhibited in the presence of the inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP3A by 22.0%, 10.0%, 5.4%, and 25.9%, respectively. No clear inhibition was observed in the presence of the CYP2C19 inhibitor.

4.3.2 *In vivo*

Male rats and male dogs received a single oral dose of ^{14}C-ixazomib (0.8[5] or 0.15 mg/kg), and metabolites in plasma were investigated. In both rat and dog plasmas, ixazomib was the main radioactive component observed, and the percentage relative to the total radioactivity in plasma was 47.6% and 58.2%, respectively. Ixazomib metabolites detected in rat plasma were M10 (dehydrogenated ixazomib), M14 (structure unidentified), M8 (dehydrogenated ixazomib), M12, M1, M13 (hydroxylated M1), and M9 (dehydrogenated ixazomib). The percentages of these metabolites relative to the total radioactivity in plasma were 24.2%, 11.4%, 6.3%, 4.5%, 2.2%, 1.9%, and 1.9%, respectively.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

Results obtained from the following studies suggest that ixazomib and its metabolites are excreted mainly in feces in rats and, in dogs, in urine and feces to a similar extent. The applicant explained that the observed difference in the excretion route between dogs and rats was due to the species difference in BA of oral ixazomib [see Section "4.1.1 Single-dose studies"].

- Bile duct-cannulated and -intact male rats received a single oral dose of ^{14}C-ixazomib (0.8 mg/kg[5]), and urinary, fecal, and biliary excretion of radioactivity was investigated. In bile duct-intact rats, urinary and fecal excretion rate up to 240 hours post-dose was 26.4% and 60.2%, respectively. In bile duct-cannulated rats, urinary, fecal, and biliary excretion rate up to 72 hours post-dose was 20.4%, 35.4%, and 22.3%, respectively.

- Male dogs received a single oral dose of ^{14}C-ixazomib (0.15 mg/kg), and urinary and fecal excretion rate of radioactivity was investigated. Urinary and fecal excretion rate up to 168 hours post-dose was 35.0% and 36.7%, respectively.

4.4.2 Excretion in milk

Excretion in milk of ixazomib was not investigated. The applicant explained that ixazomib may possibly be transferred into milk, taking account of the fact that it is a weakly basic (pKa, 8.5) and highly lipophilic (logP, 2.07) low molecular weight compound.

4.5 Pharmacokinetic interactions

In this section, the concentration of ixazomib citrate is expressed in terms of ixazomib.

4.5.1 Enzyme inhibition

Based on of the following study findings and in light of C_{max} of ixazomib (0.19 μmol/L [see Section "6.2.1.1 Japanese Phase I study"]) at steady state following the administration of ixazomib at the proposed dosage regimen, the applicant explained that ixazomib is unlikely to cause pharmacokinetic interactions through the inhibition of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in its clinical use.

- The substrates[8] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) were incubated with liver microsomes in the presence of ixazomib (0.040-30 μmol/L) and NADPH to investigate the inhibitory effect of ixazomib against each CYP isoform. Ixazomib did not show clear inhibitory effect against metabolism of any of the substrates of CYP isoforms.

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7) Furafylline, sulfaphenazole, benzylnirvanol, quinidine, and azamulin were used as inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A, respectively.

8) Phenacetin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, and dextromethorphan were used as the substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively. Testosterone and midazolam were used as the substrates of CYP3A.

- Ixazomib (0.040-30 μmol/L) was preincubated with liver microsomes in the presence or absence of NADPH, followed by incubation with the substrates[8)] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) to investigate time-dependent inhibition of each CYP isoform by ixazomib. Ixazomib did not show any clear time-dependent inhibition against the metabolism of any of the substrates of CYP isoforms.

4.5.2 Enzyme induction

Human primary cultured hepatocytes were incubated with ixazomib (0.5, 2, or 5 μg/mL) for 48 hours, or with ixazomib (0.05-5 μg/mL) for 72 hours, and enzyme activity and protein expression level of CYP isoforms (CYP1A2, CYP2B6, and CYP3A) were investigated. The treatment with ixazomib did not cause any clear increase in either enzyme activity or protein expression level of any of the CYP isoforms within the ixazomib concentration range studied.

4.5.3 Transporters

The following study findings indicated that ixazomib is not a substrate of BCRP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or sodium taurocholate cotransporting polypeptide (NTCP), but is a substrate for P-gp. Because the concomitant use of ixazomib with clarithromycin, an inhibitor of P-gp, did not affect the PK of ixazomib [see Section "6.2.3.2 Interactions with clarithromycin"], the applicant explained that pharmacokinetic interactions between ixazomib and P-gp inhibitors are unlikely to occur in clinical use of ixazomib.

- Using human hepatocytes, intracellular uptake of ixazomib (1 μmol/L) was investigated. Cyclosporine A (inhibitor of OATP1B1, OATP1B3, and NTCP) did not show any clear inhibition of ixazomib uptake.

- Using Caco-2 cell lines, P-gp- or BCRP-mediated transport of ixazomib (30 μmol/L) was investigated. Efflux ratio in the absence of inhibitors and in the presence of quinidine (30 μmol/L, P-gp inhibitor), Ko143 (0.3 μmol/L, BCRP inhibitor), and GF120918 (10 μmol/L, P-gp and BCRP inhibitor) was 2.4, 1.4, 2.0, and 1.1, respectively.

Based on the following findings and in light of C_{max} of ixazomib (0.19 μmol/L [see Section "6.2.1.1 Japanese Phase I study"]) under the steady state of ixazomib administered as per the proposed dosing regimen, the applicant explained that ixazomib is unlikely to cause pharmacokinetic interactions through the inhibition of P-gp, BCRP, organic anion transporter (OAT) 1, OAT3, OATP1B1, OATP1B3, organic cation transporter (OCT) 2, multidrug and toxin extrusion (MATE) 1, or MATE2K.

- Using Caco-2 cell lines, the inhibitory effect of ixazomib (1-100 μmol/L) against P-gp-mediated transport of ^{3}H-digoxin (3 μmol/L) was investigated. Ixazomib did not show clear inhibition of P-gp-mediated transport.

- Using porcine kidney-derived LLC-PK1 cell lines expressing human BCRP, the inhibitory effect of ixazomib (1-100 μmol/L) against BCRP-mediated transport of ^{3}H-prazosin (0.01 μmol/L) was investigated. Ixazomib did not show clear inhibition against BCRP-mediated transport.

- Using mouse kidney-derived S2 cell lines expressing human OAT1 or OAT3, the inhibitory effect of ixazomib (0.1-10 μmol/L) against OAT1- or OAT3-mediated substrate[9)] transport was investigated. Ixazomib did not show clear inhibition of OAT1- or OAT3-mediated transport.

- Using human embryonic kidney-derived HEK293 cell lines expressing human OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K, the inhibitory effect of ixazomib (0.1-10 μmol/L) against OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K-mediated substrate[10)] transport was investigated.

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9) ^{3}H-*p*-aminohippuric acid (1 μmol/L) was used as substrates for OAT1 and ^{3}H-estrone-3-sulfate (0.05 μmol/L) was used as substrates for OAT3.

10) ^{14}C-metformin (10 μmol/L) was used as the substrate of OCT2, MATE1, and MATE2K, and ^{3}H-estradiol-17β-glucuronide (0.05 μmol/L) was used as the substrate of OATP1B1 and OATP1B3.

Ixazomib did not show a clear inhibitory effect against OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K.

4.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the applicant's discussions on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of ixazomib are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, the dose and the concentration of ixazomib citrate are expressed in terms of ixazomib. In *in vivo* studies, [redacted] containing sodium chloride 0.45% was used as vehicle, unless specified otherwise.

5.1 Single-dose toxicity

5.1.1 Single-dose oral toxicity study in rats

Rats (SD, 3 males/group) received a single oral dose of ixazomib (0.1, 0.3, or 1 mg/kg) using 10% HP-β-CD as vehicle.

No death occurred. Animals in the 1 mg/kg group showed decreased physical activity, reduced body weight gain, decreased defecation, loose stools, and soiled fur.

Accordingly, the approximate lethal dose in this study was determined to be >1 mg/kg.

5.1.2 Single oral dose toxicity study in dogs

Dogs (beagle, n = 2 males/group) received a single oral dose of ixazomib (0.021, 0.07, 0.14, or 0.21 mg/kg) using 0.5% methylcellulose as vehicle.

No death occurred. None of the groups showed any toxicologically significant changes.

Accordingly, the approximate lethal dose in this study was determined to be >0.21 mg/kg.

5.2 Repeated-dose toxicity

5.2.1 One-month repeated oral dose toxicity study in rats

Rats (SD, 15 animals/sex/group) received orally ixazomib (0 [vehicle, [redacted] containing propylene glycol 1%], 0.4, 0.8, 1.0 [female only], 1.2 mg/kg [male only]) twice weekly for 2 weeks, followed by a 10-day withdrawal period. The treatment cycle of 21 days was repeated twice for a total of 1 month. More than 1 male animal in the 1.2 mg/kg group died after the first dose in Cycle 1, the dose in the male animals of the 1.2 mg/kg group was reduced to 1.0 mg/kg from the second dose onward. Subsequently, dosing ixazomib began in female animals at ≤1.0 mg/kg. However, it was terminated after >1 female animal in the 1.0 mg/kg group had died. Five each of males and females in each dose group had a 14-day recovery period after the completion of administration.

Death occurred in 5 of 15 females in the 1.0 mg/kg group and in 6 of 15 males in the 1.2 mg/kg group. The dead animals showed decreased physical activity, coldness, labored respiration, hunched position, mucous feces, loose stools, abnormalities of body fluid and electrolytes, acute intestinal inflammation and mucosal hypertrophy, thymic cortical cell necrosis and decreased cell count, necrosis and vacuolization of adrenocortical fasciculata cells, vacuolization of hepatocytes, decreased bone marrow cell count, and lymphocyte depletion in spleen and lymphatic tissues. The cause of deaths was metabolic stress due to intestinal toxicity.

Surviving animals in the ≥0.4 mg/kg groups suffered increased liver weight, intestinal mucosal hypertrophy and acute inflammation, gastric distention, decreases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, and blood urea nitrogen (BUN), increases in white blood cell count and neutrophil count, and vacuolization of adrenal cortical cells. Surviving animals in the ≥0.8 mg/kg groups showed decreased body weight and decreased food consumption, decreased cholesterol, increases in monocyte count, basophil count, and fibrinogen, increased adrenal weight, shrinkage and weight decrease of thymus, lymphocyte depletion in lymphatic tissues, decreased thymic cortex cells,

increased bone marrow cell count, increased myeloid cell/erythroid cell ratio, and decreased lymphocyte count.

All changes were reversible or tended to be reversible after the 14-day recovery period.

Accordingly, the no observed adverse effect level (NOAEL) in this study was determined to be <0.4 mg/kg, and the maximum tolerated dose to be 0.8 mg/kg.

5.2.2 Three-month repeated oral dose toxicity study in rats

Rats (SD, 10-15 animals/sex/group) received oral ixazomib (0 [vehicle], 0.2, 0.4, 0.8 mg/kg) twice weekly for 2 weeks, followed by a 10-day withdrawal period. The treatment cycle of 21 days was repeated 5 times for 3 months. Because >1 animal in the 0.8 mg/kg group died at the end of Cycle 2, the dose in this group was reduced to 0.6 mg/kg from Cycle 3 onward. Five each of males and females in the 0, 0.4, and 0.8 mg/kg groups had a 14-day recovery period after the completion of the treatment period.

Death occurred in 2 of 30 animals in the 0.8 mg/kg group. The dead animals showed decrease in physical activity, cutis laxa, emaciation, pallor of limbs, coldness, labored respiration, decreased defecation, degeneration of gastrointestinal epithelia, single cell necrosis and acute inflammation of intestinal epithelium, degeneration of germ cells in testis, as well as decreased cell density, single cell necrosis, and lymphocyte depletion in bone marrow. The causes of deaths were degeneration of gastrointestinal epithelia, single cell necrosis and acute inflammation of intestinal epithelium, and sepsis caused by decreased cell density, single cell necrosis, and lymphocyte depletion in bone marrow.

Surviving animals in the ≥0.2 mg/kg groups suffered increased adrenal and liver weight, epithelial hyperplasia, single cell necrosis and acute inflammation of small intestine, and single cell necrosis and lymphocyte depletion in lymphatic tissues. Surviving animals in the 0.4 mg/kg group had germ cell degeneration and seminiferous tubule necrosis in testis. Changes observed in the ≥0.4 mg/kg groups were decreased food consumption, increases in white blood cell count, neutrophil count, lymphocyte count, basophil count, and glucose concentration in blood, decreases in BUN, ALP, eosinophil count, and platelet count, and decreases in calcium and chloride concentrations in urine. Changes observed in the 0.8 mg/kg group were reduced body weight gain, increased monocyte count in blood, epithelial hyperplasia and acute inflammation of rectum, chronic advanced nephropathy, and increased protein in urine. The changes observed in the 0.2 mg/kg group were considered of little toxicological significance because (a) the increases in adrenal and liver weight were not associated with relevant histopathological changes and (b) the changes in the small intestine and in lymphatic tissues were minimal.

All changes were reversible or tended to be reversible after the 14-day recovery period.

Accordingly, the NOAEL in this study was determined to be 0.2 mg/kg.

5.2.3 Six-month repeated oral dose toxicity study in rats

Rats (SD, 15 animals/sex/group) received oral ixazomib (0 [vehicle], 0.2, 0.4, 0.8 mg/kg) once weekly for 3 weeks, followed by a 13-day withdrawal period. The treatment cycle of 28 days was repeated 7 times for 6 months. Because >1 female animal in the 0.8 mg/kg group died at the end of Cycle 2, the dose in this group was reduced to 0.6 mg/kg from Cycle 3 onward. Five each of males and females in each group had a 14-day recovery period after the completion of administration.

Death occurred in 7 of 15 female animals in the 0.8 mg/kg group. Dead animals showed transparent ocular discharge, perinasal red substances, yellow substances around the urogenital organ, neutrophil infiltration, epithelial hyperplasia, necrosis, and villi atrophy in the intestinal lamina propria, hepatocyte degeneration and necrosis in the liver, disseminated hepatocyte vacuolization, sinusoidal infiltration of neutrophils, lymphocyte depletion and necrosis in lymphatic tissues, decreased cell density and single cell necrosis in bone marrow, bleeding, degeneration, and necrosis of adrenal fasciculate, decreased secretory granules and single cell necrosis in adrenal medulla cells, and ulcer, degeneration, and necrosis

of tongue. It was determined that death was caused by toxicity in the intestine, liver, and lymphatic tissues.

Surviving animals in the ≥0.2 mg/kg groups suffered epithelial hyperplasia, neutrophil infiltration, and single cell necrosis in lamina propria in the large and small intestines, lymphocyte necrosis in mesenteric lymph nodes, and decreased vacuolization of adrenal cortical fasciculata cells. Those in the ≥0.4 mg/kg groups had reduced body weight gain, increases in white blood cell count, neutrophil count, lymphocyte count, monocyte count, and basophil count, enhanced mucus production in submandibular gland, subacute inflammation of glandular stomach and anterior stomach, neutrophil infiltration in splenic red pulp, and decreased cell density in bone marrow. Surviving animals in the 0.8 mg/kg group suffered transparent ocular discharge, diarrhea, loose stools, decreased defecation, decrease in physical activity, emaciation, yellow substances around urogenital organ and forelimbs, red substances around nose and mouth, erosion of glandular stomach, ulcer of anterior stomach, hyperplasia of lobular acini and enhanced secretion in mammary gland, delayed release of spermatids in testis, mononuclear perivasculitis in brain and spinal meninges, and mononuclear vasculitis in intestinal submucosa. Changes observed in the 0.2 mg/kg group were all mild and considered of little toxicological significance.

All changes were reversible or tended to be reversible after the 14-day recovery period.

Accordingly, the NOAEL in this study was determined to be 0.2 mg/kg. AUC_{168h} (483 ng·h/mL) in the 0.2 mg/kg group was 0.44 times the clinical exposure.[11)]

5.2.4 Three-month repeated oral dose toxicity study in dogs

Dogs (beagle, 3-6 animals/sex/group) received oral ixazomib (0 [vehicle], 0.05, 0.10, 0.15 mg/kg) twice weekly for 2 weeks, followed by a 10-day withdrawal period. The treatment cycle of 21 days was repeated 5 times for 3 months. Three each of males and females in the 0, 0.10, and 0.15 mg/kg groups had a 14-day recovery period after the completion of administration.

No death occurred. Animals in the ≥0.10 mg/kg groups showed neurodegeneration in sympathetic nerves, posterior roots, peripheral autonomic nerves, and ganglia of peripheral organs, as well as nerve fiber degeneration of peripheral nerves and spinal cord.

All changes were reversible or tended to be reversible after the 14-day recovery period.

Accordingly, the NOAEL in this study was determined to be 0.05 mg/kg.

5.2.5 Nine-month repeated oral dose toxicity study in dogs

Dogs (beagle, 3-6 animals/sex/group) received oral ixazomib (0 [vehicle], 0.05, 0.10, 0.20 mg/kg) once weekly for 3 weeks, followed by a 13-day withdrawal period. The treatment cycle of 28 days was repeated 10 times for 9 months. Three each of males and females in the 0, 0.10, and 0.20 mg/kg groups had a 14-day recovery period after the completion of administration.

No death occurred. Animals in the ≥0.10 mg/kg groups suffered neutrophil infiltration in the stomach and intestine. Those in the 0.20 mg/kg group showed stomach erosion, increased AST, decreases in lymphocyte count and phosphate, neutrophil infiltration and lymphocyte depletion in lymphatic tissues, neurodegeneration in sympathetic nerves, posterior roots, and ganglia of peripheral organs, nerve fiber degeneration of peripheral nerves, ascending tract of dorsal column of spinal cord, and cerebellomedullary white matter tract, as well as gliosis of the dorsal column of spinal cord and the white matter tract of the brain. Neutrophil infiltration in the stomach and intestine observed in the 0.10 mg/kg group was minimal and considered of little toxicological significance.

Except nerve fiber degeneration in the lumbar dorsal root ganglion observed in the 0.20 mg/kg group, all changes were reversible or tended to be reversible after the 14-day recovery period.

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11) Following a once-weekly oral dose of ixazomib (4.0 mg) for 3 weeks to Japanese patients with relapsed or refractory MM, AUC_{168h} was 1086 ng·h/mL (Study TB-MC010034).

Accordingly, the NOAEL in this study was determined to be 0.10 mg/kg. AUC_{168h} (1940 ng·h/mL) in the 0.10 mg/kg group was 1.8 times the clinical exposure.[11)]

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral lymphocytes, and *in vivo* genotoxicity studies consisted of a mouse bone marrow micronucleus assay and a comet assay using the liver and glandular stomach.

The reverse mutation assay, micronucleus assay, and comet assay were all negative. The chromosomal aberration assay showed an increase in chromosome structural abnormalities, whereas the micronucleus assay did not show micronucleus induction and the comet assay did not show DNA damage induction. The applicant explained that the results indicate a low risk of chromosomal aberrations induced by ixazomib in its clinical use.

5.4 Carcinogenicity

Because ixazomib is an antineoplastic drug intended to treat patients with advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Embryo-fetal development studies were conducted in rats and rabbits to investigate reproductive and developmental toxicity.

5.5.1 Fertility and early embryonic development to implantation

Because ixazomib is an antineoplastic drug intended to treat patients with advanced cancer, studies on fertility and early embryonic development to implantation were not conducted.

5.5.2 Embryo-fetal development in rats

Pregnant rats (SD, 20 animals/group) received oral ixazomib (0 [vehicle], 0.2, 0.4, 0.6 mg/kg) on Gestation Days 6, 9, 12, and 15.

Death occurred in 2 of 20 animals in the 0.6 mg/kg group. Dead animals showed decreased defecation and soiled fur.

Changes observed in maternal animals were decreased body weight and decreased food consumption in the ≥0.2 mg/kg groups, thymic atrophy in the ≥0.4 mg/kg groups, and black spots on gastric mucosal surface in the 0.6 mg/kg group. No effects on embryos or fetuses were observed.

Based on the above, the NOAEL in this study was determined to be <0.2 mg/kg for general toxicity in maternal animals and 0.6 mg/kg for embryo-fetal development. AUC_{72h} at the NOAEL for embryo-fetal development was 1103 ng·h/mL, which was higher than the clinical exposure.[12)]

5.5.3 Embryo-fetal development in rabbits

Pregnant rabbits (NZW, 20 animals/group) received oral ixazomib (0 [vehicle, [redacted] containing glycine 3%], 0.1, 0.3, 1.0 mg/kg) on Gestation Days 7, 10, 13, 16, and 19.

No death occurred. Changes observed in maternal animals were decreased body weight, decreased food consumption, and reduced body weight gain in the ≥0.3 mg/kg groups and loose stools and soiled fur in the 1.0 mg/kg group. Changes observed in embryos and fetuses were variations in lumbar vertebral count and full supernumerary ribs in the ≥0.3 mg/kg groups and caudal vertebral abnormalities and brachyury in the 1.0 mg/kg group.

12) Following a once-weekly oral administration of ixazomib (4.0 mg) for 3 weeks to Japanese patients with relapsed or refractory MM, AUC_{72h} was 738 ng·h/mL (Study TB-MC010034).

Based on the above, the NOAEL in this study was determined to be 0.1 mg/kg for general toxicity in maternal animals and for embryo-fetal development. AUC_{72h} at the NOAEL for embryo-fetal development was 497 ng·h/mL, which was 0.67 times the clinical exposure.[12)]

5.6 Other studies

5.6.1 Phototoxicity (Reference data)

In an *in vitro* phototoxicity test using mouse 3T3 fibroblasts, cytotoxicity of ixazomib was evaluated with or without UV-A irradiation. Photoirradiation factor was 1.54, suggesting that ixazomib has no phototoxicity.

Accordingly, it was determined that ixazomib is unlikely to have phototoxicity.

5.6.2 Safety evaluation of impurities

[redacted] is an impurity contained in the drug substance. The amount exceeding the qualification threshold is unlikely to pose safety concerns, based on the following study results:

- In the 1-month repeated oral dose toxicity study of ixazomib in rats [see Section "5.2.1 One-month repeated oral dose toxicity study in rats"], ixazomib was administered to the 0.8 mg/kg group at a dose equal to or greater than the maximum clinical dose[13)] of [redacted]. The treatment was well tolerated.

- The daily maximum clinical dose of [redacted] is <1 mg, and *in silico* analyses using Deductive Estimation of Risk from Existing Knowledge (DEREK) and Case Ultra did not suggest any concern for genotoxicity.

5.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews on nonclinical toxicity, PMDA concluded that there is no problem in the clinical use of ixazomib, except in administration in pregnant women.

5.R.1 Administration in pregnant women or women who may possibly be pregnant

In light of the following observations, the possibility cannot be excluded that a clinical dose of ixazomib may cause developmental toxicity including teratogenicity. Therefore, the applicant will highlight that (a) ixazomib should not be used to pregnant women or women who may possibly be pregnant and (b) when ixazomib is used to any of these patients out of necessity, the patient should be well informed of the risk that ixazomib may pose to the fetus.

- Rabbit embryo-fetal development studies revealed teratogenicity including caudal vertebral abnormalities and brachyury [see Section "5.5.3 Embryo-fetal development in rabbits"].

- Rabbit embryo-fetal development studies of bortezomib and carfilzomib, which have proteasome-inhibitory effect as with ixazomib, revealed fetal toxicities occurred at an equivalent dose of less than the clinical doses (see *Clin Cancer Res*. 2004;10:3954-64 and "Review Report dated April 13, 2016 Kyprolis for Intravenous Infusion 10 mg, 40 mg").

PMDA's view:
Based on the applicant's explanation, PMDA concluded that ixazomib should be contraindicated in pregnant women or women who may possibly be pregnant.

5.R.2 Testicular toxicity

Germ cell degeneration and seminiferous tubule necrosis in testis were observed in the 3-month repeated oral dose toxicity study in rats [see Section "5.2.2 Three-month repeated oral dose toxicity study in rats"]. However, no dose-response correlation was observed in surviving animals. Therefore, the applicant explained that the observed changes are unlikely to be related to ixazomib.

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13) Based on the specification limit (the maximum permitted level) of [redacted], the maximum level of [redacted] was calculated that may be contained in ixazomib 4.0 mg, the daily dose administered to humans.

PMDA's view:
In the 3-month repeated oral dose toxicity study in rats, germ cell degeneration in testis was observed in dead animals (the maximum dose group) as well [see Section "5.2.2 Three-month repeated oral dose toxicity study in rats"], suggesting a correlation between the testicular changes and ixazomib. Considering a possible effect of ixazomib on sperms, the applicant should highlight the need of precautionary advice to patients with reproductive capacity on the importance of contraceptive measures during the treatment and a certain period after treatment.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral formulations of ixazomib are available as Capsule A, Capsule B, and in liquid form. PK, etc. of ixazomib was investigated using these formulations and injection (Table 11). The commercial formulations are identical with Capsule B 2.3, 3.0, and 4.0 mg used in clinical studies.

Table 11. Formulations used in each clinical study

Formulation	Study
Capsule A (0.2, 0.5, 2.0 mg)	Foreign Phase I studies (Studies C16003, C16004, and C16009[*1])
Capsule B (0.2, 0.5, 2.0, 2.3, 3.0, 4.0 mg)	Japanese Phase I study (Study TB-MC010034[*2]), global Phase III study (Study C16010[*2]), foreign Phase I studies (Studies C16007,[*3] C16009,[*1] C16013,[*2] C16015,[*2] C16016,[*2] and C16018[*4]), foreign Phase I/II studies (Studies C16005[*2] and C16008[*2])
Oral liquid	Foreign Phase I study (Study C16016)
Injection	Foreign Phase I study (Studies C16001 and C16002)

[*1] Capsule A was used only in the study of relative BA (Group 2), and Capsule B in other studies including the food effect study (Group 3). [*2] Capsules 2.3, 3.0, and 4.0 mg were used. [*3] Capsules 0.2, 0.5, and 2.0 mg were used. [*4] Capsules 0.5, 2.3, 3.0, and 4.0 mg were used.

6.1.1 Assay

Ixazomib in human plasma, whole blood, and urine was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 0.5 ng/mL for all types of samples.

6.1.2 Relative BA (CTD 5.3.1.1-1, Study C16009, Group 2 [Ongoing since November 2011 (data cut-off, August 4, 2014)])

A two-treatment, two-period, crossover study was conducted in 20 patients with advanced solid cancer (14 patients were included in the PK analysis) to investigate relative BA between Capsules A and B of ixazomib. Each treatment cycle consisted of 28 days. In Cycle 1, relative BA was investigated with oral ixazomib (4.0 mg, Capsule A or B) administered on Days 1 and 15 under fasted conditions (fasting period, from 2 hours before ixazomib administration until 1 hour post-dose). From Cycle 2 onward, ixazomib (4.0 mg, Capsule B) was administered orally QD on Days 1, 8, and 15.

Median t_{max} of ixazomib was 1.29 and 1.25 hours with Capsules A and B, respectively. The geometric mean ratio [90% CI] of C_{max} and AUC_{216h} of ixazomib achieved with Capsule B relative to that achieved with Capsule A was 1.16 [0.84, 1.61] and 1.04 [0.91, 1.18], respectively. AUC_{216h} (geometric mean [coefficient of variation (CV) %]) in the Period 1 (Day 1) and the Period 2 (Day 15) in Cycle 1 was 1066 (51.3) and 1547 (62.6) ng·h/mL, respectively, with Capsule A, and 1057 (36.9) and 1800 (72.0) ng·h/mL, respectively, with Capsule B. Based on these results, the applicant explained that the exposure was greater in the Period 2 than in the Period 1.

6.1.3 Food effect (CTD 5.3.1.1-1, Study C16009, Group 3 [Ongoing since November 2011 (data cut-off, August 4, 2014)])

A two-treatment, two-period crossover study was conducted in 24 patients with advanced solid caner, malignant lymphoma, or Waldenström's macroglobulinemia (WM) (15 patients were included in the PK analysis) in order to investigate the effect of food on the PK of ixazomib. Each treatment cycle consisted of 28 days. In Cycle 1, food effect was investigated with ixazomib (4.0 mg) administered orally on Days 1 and 15 under fasting conditions (fasting period, from ≥10 hours before administration until ≥4 hours post-dose) or at 30 minutes after consumption of a high-fat diet (fat accounting for approximately 50%

of total calorie of approximately 800-1000 kcal). From Cycle 2 onward, ixazomib (4.0 mg) was administered orally QD on Days 1, 8, and 15.

Median t_{max} of ixazomib was 1.0 and 4.0 hours, respectively, following administration under fasted conditions and following administration after a high-fat diet. The geometric mean ratio [90% CI] of C_{max} and AUC_{216h} achieved with administration after a high-fat diet relative to that achieved with administration under fasted conditions was 0.31 [0.21, 0.45] and 0.72 [0.58, 0.89], respectively. The delayed t_{max} of ixazomib and decreased exposure in administration after a high-fat diet compared with administration under fasted conditions were likely caused by the decreased gastric emptying rate associated with the intake of a high-fat diet (*Clinical Pharmacokinetics*. 1999;37:213-55). AUC_{216h} (geometric mean [CV%]) in the Period 1 (Day 1) and the Period 2 (Day 15) in Cycle 1 was 1073 (22.6) and 1927 (40.4) ng·h/mL, respectively, in administration under fasted conditions and 625 (61.3) and 1705 (61.4) ng·h/mL, respectively, in administration after a high-fat diet. Based on the above results, the applicant explained that the exposure increased in Period 2 compared with Period 1.

In the above studies of relative BA and food effect, the exposure increased in Period 2 as compared with Period 1. The applicant however explained that the cause of the increase was unclear.

6.1.4 Effect of gastric pH on the PK of ixazomib

The solubility of ixazomib was 3.0 to 10.1 mg/mL within the pH range studied (1.5-9.1), increasing with pH. The dissolution rate of ixazomib measured using Capsule B (4.0 mg) was ≥85% in 30 minutes over the pH range of 1.2 to 6.8. Based on these results, the applicant explained that increased gastric pH due to low gastric acidity or a proton pump inhibitor administered is unlikely to affect the PK of ixazomib.

6.2 Clinical pharmacology

The PK of ixazomib in patients with cancer was investigated in ixazomib monotherapy as well as in combination therapy of ixazomib with DEX, lenalidomide, ketoconazole, clarithromycin, or rifampicin.

6.2.1 Japanese clinical study

6.2.1.1 Japanese Phase I study (CTD 5.3.3.3-4, Study TB-MC010034 [Ongoing since June 2012 (data cut-off, January 6, 2014)])

An open-label, uncontrolled study was conducted in 14 patients with relapsed or refractory MM (14 patients were included in the PK analysis) to investigate PK, etc. of ixazomib. In each treatment cycle of 28 days, ixazomib (4.0 mg) was administered orally QD on Days 1, 8, and 15 in combination with or without Ld regimen,[14)] and plasma ixazomib concentration was measured (Table 12). Accumulation rate[15)] in ixazomib monotherapy and in ixazomib/Ld therapy was 2.09 and 1.78, respectively, showing accumulation of ixazomib of multiple doses.

Table 12. PK parameters of ixazomib

Ld regimen	Date of measurement	n	C_{max} (ng/mL)	DN C_{max} (ng/mL/mg)	t_{max}* (h)	AUC_{168h} (ng·h/mL)	DN AUC_{168h} (ng·h/mL/mg)	$t_{1/2}$ (h)
Not used	Day 1	7	65.3 (61)	16.4 (61)	1.1 (0.5, 7.2)	1071 (79)	268 (79)	-
	Day 15	5	68.8 (68)	17.2 (68)	1.8 (0.3, 3.3)	1588 (60)	397 (60)	137 (27)
Used	Day 1	7	32.9 (52)	8.2 (52)	1.5 (1.0, 7.2)	564 (41)	141 (41)	-
	Day 15	6	34.5 (95)	8.6 (95)	1.4 (0.5, 7.1)	1086 (54)	272 (54)	125 (3)

Geometric mean (CV%); -, Not calculated; * Median (range)

6.2.2 Foreign clinical studies

6.2.2.1 Foreign Phase I study (CTD 5.3.5.2-4, Study C16004 [Ongoing since October 2009 (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in 60 patients with relapsed or refractory MM (44 patients were included in the PK analysis) to investigate PK, etc. of ixazomib. In each treatment cycle of 28 days, ixazomib (0.24-3.95 mg/m^2) was administered orally QD on Days 1, 8, and 15, and plasma ixazomib concentration was measured (Table 13). The applicant explained that exposure (AUC_{168h}) to

[14)] An oral dose regimen of lenalidomide (25 mg) from Day 1 to Day 21 and DEX (40 mg) on Days 1, 8, 15, and 22 in each treatment cycle of 28 days

[15)] The ratio of AUC_{168h} on Day 15 to AUC_{168h} on Day 1

ixazomib on Days 1 and 15 increased with dose over the dose range studied (0.8-3.95 mg/m^2). Accumulation rate[15)] in the 2.97 mg/m^2 group was 2.12.

Table 13. PK parameters of ixazomib

Dose (mg/m^2)	Date of measurement	n	C_{max} (ng/mL)	DN C_{max} (ng/mL/mg)	t_{max}[*1] (h)	AUC_{168h} (n·h/mL)	DN AUC_{168h} (ng·h/mL/mg)	$t_{1/2}$ (h)
0.24	Day 1	1	3.01	6.02	1.5	-	-	-
	Day 15	3	3.54 (26)	10.4 (61)	1.1 (1.0, 2.0)	-		-
0.48	Day 1	1	2.91	3.64	1.5	-	-	-
	Day 15	1	4.64	5.80	0.5	-		-
0.80	Day 1	2	2.84, 8.65	2.03, 6.18	1.0, 2.0	-	-	-
	Day 15	3	5.61 (74)	4.01 (74)	1.8 (1.0, 2.0)	366, 431	261, 308	271
1.20	Day 1	1	15.1	6.86	1.0	-	-	-
	Day 15	2	11.8, 24.0	6.56, 10.4	1.0, 1.0	-	-	185, 196
1.68	Day 1	3	11.9 (70)	3.48 (70)	1.5 (1.0, 2.0)	192, 324	49.2, 95.3	-
	Day 15	2	8.65, 26.6	2.22, 7.82	1.0, 1.5	562, 764	144, 225	180, 198
2.23	Day 1	2	21.2, 36.9	4.24, 8.58	1.0, 1.5	598	139	-
	Day 15	1	9.24	2.15	8.0	868	202	175
2.97	Day 1	24	69.8 (61)	12.0 (57)	1.0 (0.5, 4.0)	906[*2] (49)	161[*2] (48)	-
	Day 15	17	65.4 (61)	11.3 (60)	1.0 (0.5, 4.0)	1710[*3] (53)	288[*3] (54)	144[*4] (39)
3.95	Day 1	4	98.1 (64)	12.5 (75)	1.0 (0.5, 1.5)	1180 (53)	151 (54)	-
	Day 15	1	134	20.3	1.0	1460	221	165

Geometric mean (CV%) (individual values for n = 1 or 2); -, Not calculated; [*1] Median (range); [*2] n = 17, [*3] n = 10, [*4] n = 11

6.2.2.2 Foreign Phase I/II study (CTD 5.3.5.2-5, Study C16005 [Ongoing since November 2010 (data cut-off, March 8, 2013)])

An open-label, uncontrolled study was conducted in 65 patients with newly diagnosed MM (11 patients in the Phase I were included in the PK analysis) to investigate the PK, etc. of ixazomib in combination with Ld regimen.[14)] In the Phase I, ixazomib (1.68-3.95 mg/m^2) was administered orally QD in combination with Ld regimen on Days 1, 8, and 15 in each 28-day treatment cycle, and plasma ixazomib concentration was measured (Table 14). The accumulation rate[15)] in the 2.23 and 2.97 mg/m^2 groups was 1.85 and 2.05, respectively.

Table 14. PK parameters of ixazomib

Dose (mg/m^2)	Date of measurement	n	C_{max} (ng/mL)	DN C_{max} (ng/mL/mg)	t_{max}[*1] (h)	AUC_{168h} (ng·h/mL)	DN AUC_{168h} (ng·h/mL/mg)	$t_{1/2}$ (h)
1.68	Day 1	1	49.8	13.8	1.0	603	168	-
	Day 15	2	6.76, 21.3	1.93, 5.92	1.1, 7.3	749, 930	214, 258	205, 216
2.23	Day 1	3	22.3 (52)	6.10 (49)	1.5 (1.0, 8.0)	588 (54)	161 (61)	-
	Day 15	3	31.4 (82)	8.57 (74)	1.0 (1.0, 2.0)	1080 (10)	296 (16)	157 (20)
2.97	Day 1	4	94.8 (34)	17.0 (44)	1.1 (0.5, 1.1)	923 (17)	166 (17)	-
	Day 15	4	53.5 (39)	9.62 (50)	1.0 (1.0, 2.0)	1830[*2] (14)	341[*2] (10)	178 (28)
3.95	Day 1	1	124	13.8	0.3	3550	394	-
	Day 15	1	169	20.6	2.0	5240	639	84.7

Geometric mean (CV%) (individual values for n = 1 or 2); -, Not calculated; [*1] Median (range), [*2] n = 3

6.2.2.3 Foreign Phase I study (CTD 5.3.2.3-1, Study C16016 [Ongoing since March 2014 (data cut-off, December [redacted], 2014)])

An open-label, uncontrolled study was conducted in 7 patients with advanced solid cancer or malignant lymphoma (5 patients were included in the PK analysis) to investigate the mass balance. In Part A of the study investigating the mass balance, patients received ^{14}C-ixazomib (4.1 mg, liquid formulation) orally on Day 1 and ixazomib (4.0 mg) on Days 14 and 21. Radioactivity concentrations in blood, plasma, urine, and feces were investigated. In Part B of the study, patients received ixazomib (4.0 mg) orally QD on Days 1, 8, and 15 in each 28-day treatment cycle.

Table 15 shows PK parameters of plasma ixazomib, plasma radioactivity, and blood radioactivity. C_{max} and AUC of radioactivity were higher in blood than in plasma. The applicant explained that the results suggested the distribution of ixazomib and its metabolites in blood cells.

Table 15. PK parameters of ixazomib and radioactivity

Analyte	C_{max} (ng Eq./mL[*1])	t_{max}[*2] (h)	AUC_{312h} (ng Eq.·h/mL[*3])	AUC_{816h} (ng Eq.·h/mL[*3])	CLr (L/h)
Plasma ixazomib	89.1 (62)	0.5 (0.5, 0.6)	1180 (46)	-	0.119 (52)
Plasma radioactivity	78.8 (54)	0.5 (0.5, 4.0)	1720 (44)	2980 (57)	-
Blood radioactivity	182 (39)	0.6 (0.5, 2.0)	17,300 (19)	29,200 (16)	-

Geometric mean (CV%); n = 5; -, Not calculated; [*1] ng/mL for ixazomib, [*2] Median (range), [*3] ng·h/mL for ixazomib

Urinary and fecal excretion rates (percentage of the administered radioactivity) up to 34 days post-dose were 62.1% and 21.8%, respectively. Radioactivity and urinary excretion rate of ixazomib up to 7 days post-dose were 32.9% and 3.2%, respectively. The applicant explained that ixazomib is eliminated mainly by metabolism, with only minor contribution of renal excretion.

6.2.3 Drug-drug interactions

6.2.3.1 Interactions with ketoconazole (CTD 5.3.1.1-1, Study C16009 Group 1 [Ongoing since November 2011 (data cut-off, August 4, 2014)])

An open-label, uncontrolled study was conducted in 29 patients with advanced solid cancer (16 patients were included in the PK analysis) to investigate the effect of ketoconazole (CYP3A inhibitor) on the PK of ixazomib. Each treatment cycle consisted of 28 days. In Cycle 1, patients received oral ixazomib (2.5 mg) on Day 1, ketoconazole (400 mg) QD on Day 12 to Day 25, and ixazomib (2.5 mg) on Day 15 to investigate the effect of ketoconazole on the PK of ixazomib. From Cycle 2 onward, patients received oral ixazomib (4.0 mg) QD on Days 1, 8, and 15.

The geometric mean ratio [90% CI] of C_{max} and AUC_{264h} of ixazomib on Day 15 (concomitant use with ketoconazole) relative to that on Day 1 (ixazomib alone) was 1.01 [0.78, 1.30] and 2.08 [1.91, 2.27], respectively. While the exposure to ixazomib was increased by concomitant use of ketoconazole with ixazomib, the exposure in Groups 2 and 3 increased in the Period 2 as compared with the Period 1 of Study C16009 [see Sections “6.1.2 Relative BA” and “6.1.3 Food effect”]. The applicant explained that these data preclude a conclusion on the effect of ketoconazole (CYP3A inhibitor) on the PK of ixazomib.

6.2.3.2 Interactions with clarithromycin (CTD 5.3.1.1-1, Study C16009, Group 5 [Ongoing since November 2011 (data cut-off, April [redacted], 2015)])

An open-label, uncontrolled study was conducted in 21 patients with advanced solid cancer (16 patients were included in the PK analysis) to investigate the effect of clarithromycin (CYP3A inhibitor) on the PK of ixazomib. In 21 days-long Cycle 1, patients received an oral single dose of ixazomib (2.5 mg) or clarithromycin (500 mg bis in die [BID]) on Day 1 to Day 16, and ixazomib (2.5 mg) on Day 6 investigating the effect of clarithromycin on the PK of ixazomib. Cycle 2 and subsequent cycles were 28 days-long, during which patients received oral ixazomib (4.0 mg) QD on Days 1, 8, and 15.

The geometric mean ratio [90% CI] of C_{max} and AUC_{264h} of ixazomib in combination therapy with ixazomib and clarithromycin to that in ixazomib monotherapy was 0.96 [0.67, 1.36] and 1.11 [0.86, 1.43], respectively.

Taking account of the above results and the study plan that had been designed to investigate the effect of clarithromycin (CYP3A inhibitor) on the PK of ixazomib based on the results of the first dose of ixazomib, the applicant explained that concomitant use with CYP3A inhibitors does not have any clear effect on the exposure to ixazomib.

6.2.3.3 Interactions with rifampicin (CTD 5.3.1.1-1, Study C16009 Group 4 [Ongoing since November 2011 (data cut-off, August 4, 2014)])

An open-label, uncontrolled study was conducted in 18 patients with advanced solid cancer (16 patients were included in the PK analysis) to investigate the effect of rifampicin (CYP3A inducer) on the PK of ixazomib. In 21 days-long Cycle 1, patients received an oral single dose of ixazomib (4.0 mg) or rifampicin (600 mg) QD on Day 1 to Day 14 plus ixazomib (4.0 mg) on Day 8 to investigate the effect of rifampicin on the PK of ixazomib. Cycle 2 and each subsequent cycle were 28 days long, during which patients received oral ixazomib (4.0 mg) QD on Days 1, 8, and 15.

The geometric mean ratio [90% CI] of C_{max} and AUC_{last} of ixazomib in combination therapy with rifampicin to that in ixazomib monotherapy was 0.46 [0.29, 0.73] and 0.26 [0.18, 0.37], respectively.

The above results demonstrated that a CYP3A inducer reduces exposure to ixazomib when combined with ixazomib. The applicant explained that precautionary advice should be given to healthcare professionals on the concomitant use of CYP3A inducers with ixazomib.

6.2.4 Foreign Phase I study investigating the effect of renal impairment on the PK of ixazomib (CTD 5.3.3.3-2, Study C16015 [Ongoing since September 2013 (data cut-off, [redacted])])

An open-label, uncontrolled study was conducted in 41 patients with advanced solid cancer or relapsed or refractory MM who had (a) normal renal function, (b) severe renal impairment, or (c) end-stage renal failure (20 in group (a), 14 in group (b), 7 in group (c); 18, 14, and 6 each of them included in the PK analysis) to investigate the effect of renal impairment on the PK of ixazomib. In Part A of the study, patients received an oral single dose of ixazomib (3.0 mg) to investigate the effect of renal impairment on the PK of ixazomib. In Part B of 28-day treatment cycles, patients received oral ixazomib QD at a dose of 2.3, 3.0, or 4.0 mg, selected according to the tolerability in Part A, on Days 1, 8, and 15. Patients also received oral DEX (20 or 40 mg) QD on Days 1, 8, 15, and 22, as necessary.

Table 16 shows PK parameters of ixazomib. C_{max} and AUC_{last} of ixazomib unbound to plasma proteins, compared with those in patients with normal renal function, were 1.60 and 1.39 times, respectively, higher in patients with severe renal impairment, 0.71 and 1.34 times, respectively, in patients with end-stage renal failure, and 1.25 and 1.38 times, respectively, in patients with severe and end-stage renal failure combined. Plasma protein-unbound rate assessed using plasma before ixazomib administration was 1.32% in patients with normal renal function, 1.20% in patients with severe renal impairment, and 1.28% in patients with end-stage renal failure, showing no clear effect of renal impairment on the plasma protein-unbound rate.

In patients with end-stage renal failure undergoing hemodialysis, plasma ixazomib concentration was measured before and after introduction of blood to the dialyzer. No clear difference was observed in plasma ixazomib concentration between before and after introduction of blood into the dialyzer, indicating that ixazomib is not removed by hemodialysis.

Table 16. PK parameters of ixazomib, classified by severity of renal impairment

Severity of renal impairment[*1]	n	Analyte	C_{max} (ng/mL)	t_{max}[*2] (h)	AUC_{last} (ng·h/mL)
Normal	18	Bound form + unbound form	25.8 (56)	1.0 (0.5, 4.0)	575[*3] (38)
		Unbound form	0.30 (66)		6.64[*3] (61)
Severe	14	Bound form + unbound form	45.3 (81)	1.0 (0.5, 1.5)	813[*4] (51)
		Unbound form	0.48 (86)		9.25[*4] (55)
End-stage renal failure	6	Bound form + unbound form	18.7 (82)	1.3 (1.0, 7.0)	783 (35)
		Unbound form	0.21 (57)		8.93 (55)
Severe and end-stage renal failure combined	20	Bound form + unbound form	34.7 (91)	1.0 (0.5, 7.0)	802[*5] (46)
		Unbound form	0.38 (98)		9.13[*5] (54)

Geometric mean (CV%) [*1] Normal, CrCL ≥90 mL/min; severe, CrCL <30 mL/min; end-stage renal failure, CrCL <30 mL/min and hemodialysis; [*2] Median (range), [*3] n = 15, [*4] n = 10, [*5] n = 16
Bound form, ixazomib bound to plasma protein; Unbound form, ixazomib unbound to plasma protein

6.2.5 Foreign Phase I study investigating the effect of hepatic impairment on the PK of ixazomib (CTD 5.3.3.3-3, Study C16018 [August 2013 to March 2015])

An open-label, uncontrolled study was conducted in 48 patients with advanced solid cancer who had (a) normal hepatic function, (b) moderate hepatic impairment, or (c) severe hepatic impairment (13 in group (a), 15 in group (b), and 20 in group (c); 12, 13, and 18 each of them included in the PK analysis) to investigate the effect of hepatic impairment on the PK of ixazomib. In Part A of the study, patients received an oral single dose of ixazomib at 4.0 mg (patients with normal hepatic function), 2.3 mg (patients with moderate hepatic impairment), or 1.5 mg (patients with severe hepatic impairment) to investigate the effect of hepatic impairment on the PK of ixazomib. In Part B of 28-day treatment cycles, patients received oral ixazomib QD on Days 1, 8, and 15 at the same dose as in Part A.

Table 17 shows PK parameters of ixazomib. C_{max} and AUC_{last} of ixazomib unbound to plasma proteins, compared with those in patients with normal hepatic function, were 1.27 and 1.32 times, respectively, higher in patients with moderate hepatic impairment, and 1.21 and 1.23 times in patients with severe hepatic impairment. Plasma protein-unbound rate assessed using plasma before ixazomib administration was 0.84%, 0.93%, and 0.98% in patients with normal hepatic function, patients with moderate hepatic impairment, and patients with severe hepatic impairment, respectively, showing no clear effect of hepatic impairment on the plasma protein unbound rate.

Table 17. PK parameters of ixazomib, classified by severity of hepatic impairment

Severity of hepatic impairment[*1]	n	Dose (mg)	Analyte	C_{max} (ng/mL)	DN C_{max} (ng/mL/mg)	t_{max}[*2] (h)	AUC_{last} (ng·h/mL)	DN AUC_{last} (ng·h/mL/mg)
Normal	12	4.0	Bound form + unbound form	61.0 (54)	15.3 (54)	1.0 (0.5, 4.0)	1160 (41)	289 (41)
			Unbound form	0.509 (47)	0.127 (47)		9.65 (50)	2.41 (50)
Moderate	13	2.3	Bound form + unbound form	42.5 (63)	18.5 (63)	1.5 (0.5, 2.5)	846[*3] (49)	368[*3] (49)
			Unbound form	0.372 (80)	0.162 (80)		7.33[*3] (61)	3.19[*3] (61)
Severe	18	1.5	Bound form + unbound form	26.1 (70)	17.4 (70)	1.2 (0.5, 4.0)	489[*4] (50)	326[*4] (49)
			Unbound form	0.232 (84)	0.154 (84)		4.44[*4] (63)	2.96[*4] (63)

Geometric mean (CV%); [*1] Classified according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria; [*2] Median (range); [*3] n = 10; [*4] n = 11; Bound form, ixazomib bound to plasma protein; Unbound form, ixazomib unbound to plasma protein

6.2.6 Relationship between exposure and change in QT/QTc interval

In foreign Phase I studies (Studies C16001, C16002, C16003, and C16004), a relationship between plasma ixazomib concentration and change from baseline in QT interval corrected by Fridericia's method (ΔΔQTcF) or that corrected by population-based correction method (ΔΔQTcP) was investigated by the linear mixed-effects model using data obtained from 245 patients in whom plasma ixazomib concentration at electrocardiogram measurement. Results did not show any clear relationship between plasma ixazomib concentration and ΔΔQTcF or ΔΔQTcP.

Based on the above, the applicant explained that ixazomib is unlikely to prolong QT/QTc interval in clinical use.

6.2.7 PPK analysis

A population pharmacokinetics (PPK) analysis was performed using the non-linear mixed-effects model (software used, NONMEM version 7.2), based on PK data of ixazomib (9907 measuring time points in 755 patients) obtained from foreign clinical studies (Studies C16001, C16002, C16003, C16004, C16005, C16007, C16008, and C16013), a Japanese clinical study (Study TB-MC010034), and a global study (Study C16010). The PK of ixazomib was described by a 3-compartment model with first order absorption process and first order elimination process.

In this analysis, possible covariates for CL were age, body surface area (BSA), race, sex, body weight, route of administration, interval of administration, serum albumin, ALT, AST, bilirubin, creatinine clearance (CrCL), hematocrit, hemoglobin, concomitant use of lenalidomide and DEX, concomitant use of potent or moderate CYP1A2 inhibitors or inducers, concomitant use of potent or moderate CYP3A4 inhibitors or inducers, and smoking habit. Possible covariates for volume of the second peripheral compartment (V4) were age, BSA, sex, serum albumin, hematocrit, and hemoglobin. However, the analysis revealed that none of them were significant covariates for CL whereas BSA was identified as a significant covariate for V4. Not selecting BSA as a significant covariate for CL suggests that BSA does not affect the exposure to ixazomib. The applicant explained that BSA is unlikely to have any clinically significant effect on the PK of ixazomib.

6.2.8 Relationship of exposure to ixazomib with efficacy and safety

Based on the data obtained from the global Phase III study (Study C16010), a relationship between exposure to ixazomib (AUC [mean per day])[16] and efficacy or safety was investigated.

6.2.8.1 Relationship between exposure and efficacy

A relationship between exposure to ixazomib (AUC [mean per day]) and progression-free survival (PFS) was investigated using a proportional hazards regression model. No clear relationship was observed between AUC (mean per day) and PFS.

6.2.8.2 Relationship between exposure and safety

A relationship between exposure to ixazomib (AUC [mean per day]) and adverse events, namely, Grade ≥3 anaemia, neutropenia, and thrombocytopenia, Grade ≥2 diarrhoea, fatigue, nausea, neuropathy peripheral, rash, and vomiting, was investigated using a multivariate logistic regression model. A significant relationship was observed between AUC (mean per day) and all adverse events except Grade ≥3 neutropenia. The incidences of these adverse events increased with increasing exposure (AUC [mean per day]).

6.2.9 Difference in PK between Japanese and non-Japanese patients

The applicant's view is that there is no clear difference in the PK of ixazomib between Japanese and non-Japanese patients because of the following reasons:

- Difference in the PK of ixazomib between Japanese and non-Japanese patients was investigated based on the PK data obtained from the Japanese Phase I study (Study TB-MC010034) [see Section "6.2.1.1 Japanese Phase I study"] and the foreign Phase I study (Study C16005) [see Section "6.2.2.2 Foreign Phase I/II study"]. The dose-adjusted exposure to ixazomib (C_{max} and AUC) in ixazomib/Ld therapy was similar between Japanese and non-Japanese patients.
- The PPK analysis showed that race was not a significant covariate for PK parameters of ixazomib [see Section "6.2.7 PPK analysis"].

6.R Outline of the review conducted by PMDA

6.R.1 Food effect

The applicant's explanation about the timing of ixazomib administration:
Results of Study C16009 showed that the exposure to ixazomib was lower in administration under fed conditions than in administration under fasted conditions [see Section "6.1.3 Food effect"]. In the global Phase III study (Study C16010) and other studies in which the timing of ixazomib was "≥1 hour before meals or ≥2 hours after meals," clinical benefits of ixazomib was demonstrated.

Accordingly, ixazomib should not be administered for 1 hour before until 2 hours after meal, and this should be communicated to healthcare professionals through the package insert in an appropriate manner [see Section "7.R.6 Dosage and administration"].

PMDA accepted the explanation of the applicant.

6.R.2 Ixazomib administration in patients with renal impairment

The applicant's explanation about the use of ixazomib in patients with renal impairment:
No clinical study was conducted to investigate PK of ixazomib in patients with mild to moderate renal impairment. For the following reasons, dose adjustment of ixazomib is unnecessary for these patients:

- In PPK analysis, CrCL was not selected as a significant covariate for PK parameters of ixazomib [see Section "6.2.7 PPK analysis"].
- In the global Phase III study (Study C16010), the incidences of all adverse events were 96% in patients with normal renal function, 100% in patients with mild renal impairment, and 99% in those with moderate renal impairment. The incidences of Grade ≥3 adverse events were 69% in patients with normal renal function, 78% in patients with mild renal impairment, and 72% in those with

[16] Estimated value based on the PPK analysis [see Section "6.2.7 PPK analysis"]

moderate renal impairment. Serious adverse events occurred in 39% of patients with normal renal function, 50% of patients with mild renal impairment, and 49% of patients with moderate renal impairment. These results do not indicate clear difference between patients with normal renal function and patients with mild or moderate renal impairment.

In contrast, for patients with severe renal impairment and those with end-stage renal failure requiring hemodialysis, treatment with ixazomib should be started at a reduced dose of 3.0 mg for the following reasons. This caution should be given in the "Precautions for Dosage and Administration" section.

- Results of Study C16015 suggest that AUC following ixazomib (3.0 mg) administration in patients with severe renal impairment and patients with end-stage renal failure requiring hemodialysis is similar to that following ixazomib (4.0 mg) administration in patients with normal renal function [see Section "6.2.4 Foreign Phase I study investigating the effect of renal impairment on PK of ixazomib"].
- No clear relationship was observed between exposure to ixazomib and PFS prolongation, while there was a relationship between exposure to ixazomib and the incidences of adverse events (Grade ≥3 anaemia and thrombocytopenia, and Grade ≥2 diarrhoea, fatigue, nausea, neuropathy peripheral, rash, and vomiting) [see Section "6.2.8 Relationship of exposure to ixazomib with efficacy and safety"].

PMDA's view:
PMDA accepted the explanation of the applicant about patients with mild and moderate renal impairment.

Patients with severe renal impairment (including patients with end-stage renal failure requiring hemodialysis) may have increased exposure to ixazomib based on the results of Study C16015. However, since no clinical data are available on the efficacy or safety of ixazomib (3.0 mg) in these patients, appropriateness of the above dose is unclear at the current moment. Therefore, information on the effect of renal impairment on PK of ixazomib, obtained in Study C16015, should be provided to healthcare professionals using the package insert, etc. Also, a caution should be provided in the" Precautions for Dosage and Administration" section to consider dose reduction in administering ixazomib to these patients and to carefully monitor patient condition for adverse events during the period of ixazomib administration [see Section "7.R.6 Dosage and administration"].

6.R.3 Ixazomib administration in patients with hepatic impairment

The applicant's explanation about the ixazomib administration in patients with hepatic impairment:
No clinical study was conducted to investigate the PK of ixazomib in patients with mild hepatic impairment. However, dose adjustment of ixazomib for these patients is unnecessary for the following reasons:

- In the PPK analysis, neither total bilirubin nor AST was selected as a significant covariate for PK parameters [see Section "6.2.7 PPK analysis"].
- In the global Phase III study (Study C16010), the incidences of (a) all adverse events, (b) Grade ≥3 adverse events, and (c) serious adverse events in patients with normal hepatic function and patients with mild hepatic impairment were (a) 98% and 100%, (b) 74% and 74%, and (c) 47% and 42%, respectively, showing no clear difference between patients with normal hepatic function and patients with mild hepatic impairment.

In contrast, for patients with moderate or severe hepatic impairment, treatment with ixazomib should be started at reduced dose of 3.0 mg for the following reasons. This caution should be given in the "Precautions for Dosage and Administration" section:

- The results of Study C16018 suggest that AUC in ixazomib (3.0 mg) administration in patients with moderate or severe hepatic impairment is similar to that in ixazomib (4.0 mg) administration in patients with normal hepatic function [see Section "6.2.5 Foreign Phase I study investigating the effect of hepatic impairment on the PK of ixazomib"].

- No clear relationship was observed between exposure to ixazomib and PFS prolongation, while there was a relationship between exposure to ixazomib and the incidences of adverse events (Grade ≥3 anaemia and thrombocytopenia, and Grade ≥2 diarrhoea, fatigue, nausea, neuropathy peripheral, rash, and vomiting) [see Section "6.2.8 Relationship of exposure to ixazomib with efficacy and safety"].

PMDA's view:
PMDA accepted the applicant's explanation about patients with mild hepatic impairment.

The results of Study C16018 indicate possible increased exposure to ixazomib in patients with moderate or severe hepatic impairment. However, since no clinical data are available on the efficacy or safety of ixazomib 3.0 mg in these patients, whether the dose is appropriate for this patient population is unclear at present. Therefore, the effect of hepatic impairment on the PK of ixazomib elucidated in Study C16018 should be communicated to healthcare professionals through the package insert, etc. Further, the "Precautions for Dosage and Administration" section should remind of the importance of careful consideration for patients with moderate or severe hepatic impairment during treatment including use of a reduced dose and close monitoring for adverse events [see Section "7.R.6 Dosage and administration"].

6.R.4 Pharmacokinetic interactions with lenalidomide and DEX

The applicant's explanation about pharmacokinetic interactions in ixazomib/Ld:
No clinical study was conducted to investigate pharmacokinetic interactions of ixazomib with lenalidomide or DEX. However, the following observations indicate that pharmacokinetic interactions are unlikely to occur between ixazomib and lenalidomide or DEX.

- No clear difference was observed in PK parameters of ixazomib between the foreign Phase I study of ixazomib monotherapy (Study C16004) and the foreign Phase I/II study of ixazomib/Ld therapy (Study C16005) [see Sections "6.2.2.1 Foreign Phase I study" and "6.2.2.2 Foreign Phase I/II study"].
- In the Japanese Phase I study (Study TB-MC010034), geometric means of C_{max} and AUC_{168h} in ixazomib/Ld therapy were lower than those in ixazomib monotherapy. However, the observed differences are considered due to a large coefficient of variation because of the small sample size [see Section "6.2.1.1 Japanese Phase I study"].
- Lenalidomide is not metabolized in the liver and excreted in urine mainly in the unchanged form (*Cancer Chemother Pharmacol.* 2012;69:789-97). This suggests that ixazomib is unlikely to affect the PK of lenalidomide. Although lenalidomide is known to be a substrate for P-gp (*Cancer Chemother Pharmacol.* 2014;73:869-74), the concomitant use of lenalidomide with quinidine, a P-gp inhibitor, did not affect the PK of lenalidomide (*Cancer Chemother Pharmacol.* 2014;73:1031-9) This suggests that clinical use of ixazomib with concomitant lenalidomide is unlikely to cause a P-gp inhibition-mediated pharmacokinetic interaction.
- DEX is a substrate for CYP3A (*Clin Pharmacol Ther.* 2000;68:487-94). However, ixazomib neither inhibits nor induces CYP3A [see Sections "4.5.1 Enzyme inhibition" and "4.5.2 Enzyme induction"], and is unlikely to affect the PK of DEX.

PMDA's view:
In the Japanese Phase I study (Study TB-MC010034), not only the geometric means of C_{max} and AUC_{168h} but also the distribution of their individual values tended to be lower in the ixazomib/Ld therapy[17)] than in the ixazomib monotherapy.[18)] Given these results, it is difficult to draw any clear conclusion about the pharmacokinetic interactions of ixazomib with lenalidomide or DEX. Therefore, relevant data, including published articles, should be collected further and any new findings related to the pharmacokinetic interactions of ixazomib with lenalidomide or DEX should be communicated to healthcare professionals in an appropriate manner.

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17) The ranges of C_{max} and AUC_{168h} were 16.6 to 69.5 ng/mL and 281 to 961 ng·h/mL, respectively, on Day 1, and 19.7 to 129 ng/mL and 541 to 2254 ng·h/mL, respectively, on Day 15.

18) The ranges of C_{max} and AUC_{168h} were 6.58 to 153 ng/mL and 208 to 3703 ng·h/mL, respectively, on Day 1, and 16.3 to 180 ng/mL and 753 to 3206 ng·h/mL, respectively, on Day 15.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 Japanese Phase I study, 1 global Phase III study, 7 foreign Phase I studies, and 1 foreign Phase I/II study. The applicant also submitted the results of 3 foreign Phase I studies and 1 foreign Phase I/II study as reference data. Table 18 summarizes the clinical study results submitted as evaluation and reference data.

Table 18. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Target patients	No. of subjects enrolled	Dosing regimen	Primary endpoints
Evaluation	Japan	TB-MC010034	I	Patients with relapsed or refractory MM	14	(a) Monotherapy cohort: Oral ixazomib 4.0 mg QD on Days 1, 8, and 15 of each 28-day cycle. (b) Combination therapy cohort: Ixazomib as per (a) in combination with the Ld regimen.	Safety PK
	Global	C16010	III		722 (a) 360 (b) 362	(a) Oral ixazomib 4.0 mg or (b) placebo QD on Days 1, 8, and 15 of each 28-day cycle in combination with the Ld regimen.	Efficacy Safety
	Foreign	C16009	I	Patients with advanced solid cancer, malignant lymphoma, or WM	112	1 cycle = 28 days* Cycle 1: (a) Group 1: Oral ixazomib 2.5 mg QD on Days 1 and 15, and oral ketoconazole 400 mg QD on Day 12 to day 25 (b) Group 2: Oral ixazomib (Formulation A or B, 4.0 mg) on Days 1 and 15 (c) Group 3: Oral ixazomib 4.0 mg (under fasted condition or after high-fat diet) on Days 1 and 15 (d) Group 4: Single oral ixazomib 4.0 mg or oral rifampicin 600 mg QD on Day 1 to Day 14, and oral ixazomib 4.0 mg on Day 8 (e) Group 5: Single oral ixazomib 2.5 mg or oral clarithromycin 500 mg BID on Day 1 to Day 16 and oral ixazomib 2.5 mg on Day 6 Cycle 2 onward: Oral ixazomib 4.0 mg QD on Days 1, 8, and 15.	Safety PK
		C16016	I	Patients with advanced solid cancer or malignant lymphoma	7	Part A: Oral ^{14}C-ixazomib 4.1 mg (liquid formulation) on Day 1 and oral ixazomib 4.0 mg on Days 14 and 21 Part B: 28-day cycles, oral ixazomib 4.0 mg QD on Days 1, 8, and 15.	Safety PK
		C16013	I	Patients with relapsed or refractory MM	43	Oral ixazomib 4.0 mg QD on Days 1, 8, and 15 of each 28-day cycle, in combination with the Ld regimen	Safety PK
		C16015	I	Patients with advanced solid cancer or relapsed or refractory MM who had normal or severely impaired renal function	41	Part A: Single oral ixazomib 3.0 mg Part B: Oral ixazomib 2.3, 3.0, or 4.0 mg QD on Days 1, 8, and 15 of each 28-day cycle	Safety PK
		C16018	I	Patients with advanced solid cancer or hematopoietic malignancy who had normal or impaired hepatic function	48	Part A: Single oral Ixazomib 1.5, 2.3, or 4.0 mg Part B: Oral ixazomib 1.5, 2.3, or 4.0 mg QD on Days 1, 8, and 15 of each 28-Day cycle	Safety PK
		C16003	I	Patients with relapsed or refractory MM	60	Oral ixazomib 0.24 to 2.23 mg/m^2 QD on Days 1, 4, 8, and 11of each 21-Day cycle	Safety Efficacy PK

Data category	Region	Study ID	Phase	Target patients	No. of subjects enrolled	Dosing regimen	Primary endpoints
		C16004	I	Patients with relapsed or refractory MM	60	Oral ixazomib 0.24 to 3.95 mg/m^2 QD on Days 1, 8, and 15 of each 28-Day cycle	Safety Efficacy PK
		C16005	I/II	Patients with newly diagnosed MM	65	(a) Phase I: Oral ixazomib 1.68 to 3.95 mg/m^2 QD on Days 1, 8, and 15 of each 28-Day cycle, in combination with the Ld regimen (b) Phase II: Oral Ixazomib 4.0 mg QD as per (a)	Safety Efficacy PK
Reference	Foreign	C16001	I	Patients with advanced solid cancer	116	Intravenous ixazomib 0.125 to 2.34 mg/m^2 on Days 1, 4, 8, and 11 of each 21-day cycle	Safety PK
		C16002	I	Patients with malignant lymphoma	31	Intravenous ixazomib 0.125 to 3.11 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle	Safety PK
		C16007	I	Patients with relapsed or refractory light chain amyloidosis	27	Oral ixazomib 4.0 or 5.5 mg QD on Days 1, 8, and 15 of each 28-day cycle	Safety PK
		C16008	I/II	Patients with newly diagnosed MM	64	(a) Phase I: Oral ixazomib 3.0 or 3.7 mg QD on Days 1, 4, 8, and 11 of each 21-day cycle, in combination with lenalidomide and DEX (b) Phase II: Oral ixazomib 3.0 mg QD as per (a)	Safety PK

[*] In Groups 4 and 5, the duration of Cycle 1 was 21 days.

The outline of each clinical study was described below.

Main adverse events observed in each clinical study except death are summarized in Section "7.3 Adverse events etc. observed in clinical studies," and PK-related data in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese Phase I study (CTD 5.3.3.3-4, Study TB-MC010034 [Ongoing since June 2012 (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with relapsed or refractory MM (target sample size, 12-24 subjects) at 5 centers in Japan.

In each 28-day treatment cycle, patients received oral ixazomib (4.0 mg) QD alone or in combination with the Ld regimen[14)] on Days 1, 8, and 15.
All of 14 patients enrolled in the study (7 each in the ixazomib monotherapy cohort and in the combination therapy cohort) received ixazomib and were included in the safety analysis. Of these, 12 patients (6 each in the monotherapy cohort and in the combination therapy cohort) were included in the analysis of dose limiting toxicity (DLT). The remaining 1 patient in the monotherapy cohort discontinued the study without receiving ixazomib on Day 15 in Cycle 1, and 1 patient in the combination therapy cohort was found to meet exclusion criteria after enrollment.

During Cycle 1 in which DLT was evaluated, DLT was observed in 1 of 6 patients in the monotherapy cohort (Grade 3 diarrhoea/nausea/hypokalaemia/hyponatraemia/hypertension/Grade 4 thrombocytopenia) and in 1 of 6 patients in the combination therapy cohort (Grade 4 thrombocytopenia/neutropenia).

The safety analysis revealed that there was no death during treatment or within 30 days after the last dose.

7.1.2 Global study

7.1.2.1 Global Phase III study (CTD 5.3.5.1-1, Study C16010 [Ongoing since August 2012 (data cut-off, July 12, 2015)])

A double-blind, randomized, comparative study was conducted to compare the efficacy and safety between the ixazomib/Ld group and the placebo/Ld group in patients with relapsed or refractory MM (target sample size, 703 subjects) in 147 centers in 26 countries including Japan.

In each 28-day treatment cycle, patients received ixazomib (4.0 mg) or placebo orally QD on Days 1, 8, and 15 in combination with the Ld regimen.[14)] Patients continued the treatment unless they met the criteria for study discontinuation.

All of 722 patients who were enrolled and randomized (360 in the ixazomib/Ld group, 362 in the placebo/Ld group) were included in the intent-to-treat (ITT) population and subjected to efficacy analysis. Of the ITT population, 720 patients treated with the study drug (361 in the ixazomib/Ld group, 359 in the placebo/Ld group)[19)] were included in the safety analysis.

The primary endpoint of the study was PFS assessed by independent review committee (IRC) according to International Myeloma Working Group (IMWG) criteria (*Blood.* 2011;117:4691-5). Three interim analyses were planned in this study. The first interim analysis was conducted at a time point when approximately 262 PFS events had occurred for the interim analysis of PFS and the first interim analysis of overall survival (OS), a secondary endpoint. The second interim analysis was planned to be conducted when approximately 365 PFS events had occurred for the final analysis of PFS and the second interim analysis. The third interim analysis was conducted based on approximately 322 OS events occurred for the third interim analysis of OS. The type 1 error associated with the interim analyses was corrected for PFS and OS using the O'Brien-Fleming type alpha spending function by Lan and DeMets. Only when PFS was significant, test for OS was performed.

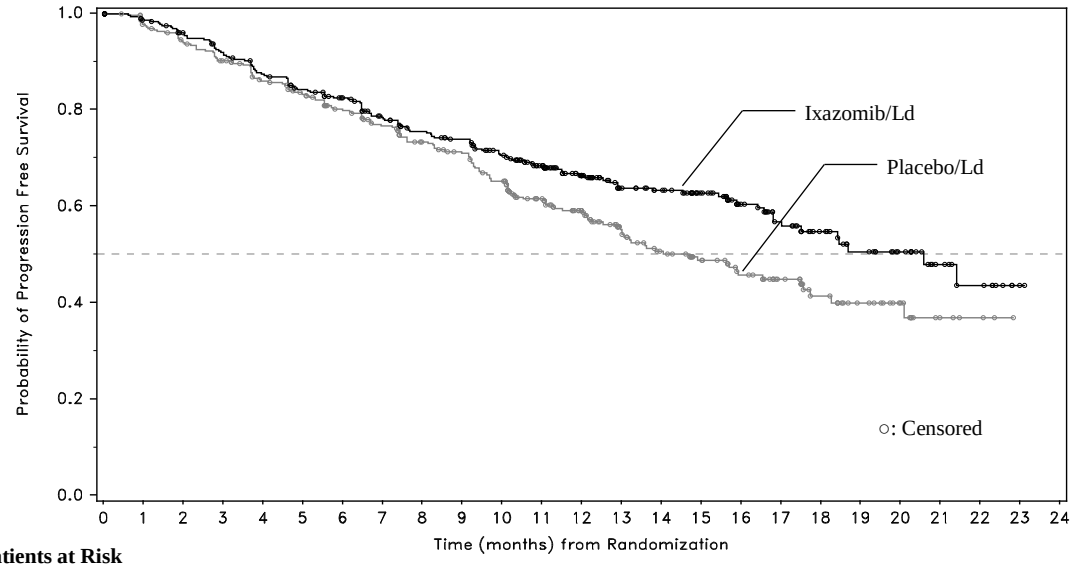
Table 19 shows PFS assessed by IRC based on IMWG criteria at the first interim analysis (data cut-off, October 30, 2014), and Figure 2 shows Kaplan-Meier curves of PFS. The data monitoring committee confirmed a significant prolongation of PFS in the ixazomib/Ld group as compared with the placebo/Ld group.

Table 19. PFS in the first interim analysis (ITT population, IRC assessment, data cut-off October 30, 2014)

	Ixazomib/Ld	Placebo/Ld
Number of patients	360	362
Number of death or aggravation (%)	129 (35.8)	157 (43.4)
Median [95% CI] (months)	20.6 [17.0, NE]	14.7 [12.9, 17.6]
Hazard ratio[*1] [95% CI]	0.74 [0.59, 0.94]	
P value (two-sided)[*2]	0.012	

[*1] Stratified Cox proportional hazard model with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (yes, no), and ISS stage at the screening (1 or 2, 3) as the stratification factors.
[*2] Stratified log-rank test with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (yes, no), and ISS stage at the screening (1 or 2, 3) as the stratification factors. Significance level of 0.02268 (two-sided).

[19)] Of 722 patients enrolled, 358 in the ixazomib/Ld group and 362 in the placebo/Ld group received the study drug. Three patients in the placebo/Ld group received mistakenly ixazomib in some of the treatment cycles and were therefore included in the ixazomib/Ld group in the safety analysis.



Number of Patients at Risk

Placebo/Ld	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0
Ixazomib/Ld	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0

Figure 2. Kaplan-Meier curves of PFS in the first interim analysis (ITT population, IRC assessment, data cut-off October 30, 2014)

The safety analysis revealed deaths of 15 of 361 patients (4.2%) in the ixazomib/Ld group and 23 of 359 patients (6.4%) in the placebo/Ld group during treatment with the study drug or within 30 days after the last dose. The causes of death other than disease progression (3 in the ixazomib/Ld group, 3 in the placebo/Ld group) were cardiac arrest, myocardial infarction, cardiovascular insufficiency, coma/cerebrovascular accident, pulmonary embolism, pneumonia, pneumonia aspiration, pneumonia fungal, acute respiratory distress syndrome, multi-organ failure, diastolic dysfunction, and sudden death (1 patient each) in the ixazomib/Ld group; and cardiac arrest (3 patients), myocardial infarction and cerebral haemorrhage (2 patients each), and cardiac failure, cardiac failure acute, cardiogenic shock, pulmonary embolism, pneumonia aspiration, pneumonia pneumococcal, pneumonia influenzal, sepsis, hypovolaemic shock, aortic dissection, cellulitis, completed suicide, and death (1 patient each) in the placebo/Ld group. A causal relationship to the study drug could not be ruled out for pulmonary embolism, pneumonia fungal, coma, and sudden death[20)] (1 patient each) in the ixazomib/Ld group, and cardiac arrest, myocardial infarction, and pulmonary embolism (1 patient each) in the placebo/Ld group.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign Phase I study (CTD 5.3.1.1-1, Study C16009 [Ongoing since November 2011 (data cut-off, August 4, 2014)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with advanced solid cancer, malignant lymphoma, or WM (target sample size, 76 subjects) at 4 centers overseas.

One treatment cycle consisted of 28-days.[21)] In Cycle 1, patients are divided into 5 groups. Group 1 received oral ixazomib (2.5 mg) on Days 1 and 15 and oral ketoconazole (400 mg) QD on Day 12 to Day 25. Patients in Group 2 received oral ixazomib (4.0 mg, Capsules A or B) on Days 1 and 15. Patients in Group 3 (fasted or fed a high-fat diet) received oral ixazomib (4.0 mg) on Days 1 and 15. Group 4 received a single dose of oral ixazomib (4.0 mg) or oral rifampicin (600 mg) QD on Day 1 to Day 14, and oral ixazomib (4.0 mg) on Day 8. Group 5 received a single dose of oral ixazomib (2.5 mg) or oral clarithromycin (500 mg) BID on Day 1 to Day 16 plus oral ixazomib (2.5 mg) on Day 6. From Cycle 2

[20)] A 6[redacted]-years old Caucasian man with a history of ischemic heart disease and coronary artery bypass. Grade 2 myocardial ischaemia was noted on Day 2 of Cycle 15. His sudden death occurred on Day 5 of Cycle 30. Whether autopsy had been performed was unclear, with the cause of death remaining unknown.

[21)] 21 days in Cycle 1 of Groups 4 and 5

onward, patients in all groups received oral ixazomib at the starting dose[22] of 4.0 mg QD on Days 1, 8, and 15.

All of 112 patients enrolled in the study received ixazomib and were included in the safety analysis.

The safety analysis revealed deaths of 2 of 29 patients (6.9%) in Group 1, 1 of 20 patients (5.0%) in Group 2, and 3 of 24 patients (12.5%) in Group 3 during treatment with ixazomib or within 30 days after the last dose. No death occurred in Group 4 or 5. All deaths were due to disease progression, and a causal relationship of the deaths to the study drug was ruled out.

7.1.3.2 Foreign Phase I study (CTD 5.3.2.3-1, Study C16016 [Ongoing since March 2014 (data cut-off, December [redacted], 2014)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with advanced solid cancer or malignant lymphoma (target sample size, 10 subjects) at a single center overseas.

In Part A of the study, patients received ^{14}C-ixazomib (liquid formulation, 4.1 mg) orally on Day 1 and oral ixazomib (4.0 mg) on Days 14 and 21. In Part B, patients received oral ixazomib (4.0 mg) QD on Days 1, 8, and 15 in each 28-day cycle and continued to receive treatment unless they meet any of the criteria for study withdrawal.

All of 7 patients enrolled in the study received the study drug and were included in the safety analysis.

The safety analysis revealed no death during treatment or within 30 days after the last dose.

7.1.3.3 Foreign Phase I study (CTD 5.3.3.3-1, Study C16013 [Ongoing since December 2012 (data cut-off, July 14, 2014)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with relapsed or refractory MM (target sample size, 24 subjects) at 8 centers overseas.

In each 28-day treatment cycle, patients received oral ixazomib (4.0 mg) QD on Days 1, 8, and 15 in combination with the Ld regimen.[14] Patients continued to receive treatment unless they meet any of the criteria for study withdrawal.

All of 43 patients enrolled in the study received ixazomib and were included in the safety analysis.

The safety analysis revealed no death during treatment with ixazomib or within 30 days after the last dose.

7.1.3.4 Foreign Phase I study (CTD 5.3.3.3-2, Study C16015 [Ongoing since September 2013 (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with advanced solid cancer or relapsed or refractory MM who had normal or severely impaired renal function (target sample size, 28 subjects) at 6 centers overseas.

In Part A of the study, patients received a single oral dose of ixazomib (3.0 mg). In Part B with treatment cycles of 28 days, patients received oral ixazomib at a dose of 2.3, 3.0, or 4.0 mg QD, which were selected based on the tolerability in Part A, on Days 1, 8, and 15 of each 28-days cycle. In addition, patients with relapsed or refractory MM received oral DEX (20 or 40 mg) QD on Days 1, 8, 15, and 22 as necessary.

All of 41 patients enrolled in the study (20 patients with normal renal function, 14 patients with severe renal impairment, and 7 patients with end-stage renal failure) received ixazomib and were included in the safety analysis.

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[22] In the initial version of the study protocol, the dose in Cycle 2 and succeeding cycles was 5.5 mg. The starting dose was reduced to 4.0 mg in the revised first edition. The maximum dose for dose titration was changed to 5.3 mg in the revised second edition.

The safety analysis revealed no death in patients with normal renal function and deaths of 2 of 14 patients with severe renal impairment (14.3%) and 1 of 7 patients with end-stage renal failure (14.3%) during treatment or within 30 days after the last dose, in. The causes of deaths were respiratory failure and pneumonia (1 patient each with severe renal impairment) and dyspnoea (1 patient with end-stage renal failure). A causal relationship of respiratory failure (1 patient) to ixazomib could not be ruled out.

7.1.3.5 Foreign Phase I study (CTD 5.3.3.3-3, Study C16018 [August 2013 to March 2015])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ixazomib in patients with advanced solid cancer who had normal or impaired hepatic function (target sample size, 36 subjects) at 4 centers overseas.

In Part A of the study, a single dose of oral ixazomib was administered at 4.0 mg to patients with normal hepatic function, at 2.3 mg to patients with moderate hepatic impairment, and at 1.5 mg to patients with severe hepatic impairment. Patients who showed tolerance in Part A were eligible to proceed to Part B, in which they received oral ixazomib QD at the same dose as in Part A on Days 1, 8, and 15 in each 28-day cycle.

All of 48 patients enrolled in the study (13 patients with normal hepatic function, 15 patients with moderate hepatic impairment, and 20 patients with severe hepatic impairment) received ixazomib and were included in the safety analysis.

The safety analysis revealed deaths of 6 of 15 patients with moderate hepatic impairment (40.0%), 8 of 20 patients with severe hepatic impairment (40.0%) during treatment or within 30 days after the last dose. None of the patients with normal hepatic function. The causes of death were hepatic failure, pulmonary embolism, septic shock, gallbladder cancer, peritoneal haemorrhage, and renal failure acute (1 patient each) in patients with moderate hepatic impairment; and acute renal failure (3 patients), acute hepatic failure, hepatic failure, pancreatic carcinoma, cholangiocarcinoma, and small cell lung cancer (1 patient each) in patients with severe hepatic impairment. A causal relationship to ixazomib was ruled out for all of these events.

7.1.3.6 Foreign Phase I study (CTD 5.3.5.2-3, Study C16003 [Ongoing since [redacted], 20[redacted] (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with relapsed or refractory MM (target sample size, approximately 70 subjects) at 5 centers overseas.

Each treatment cycle consisted of 21 days. In the dose-titration part of the study, patients received oral ixazomib (0.24, 0.48, 0.8, 1.2, 1.68, 2.0, or 2.23 mg/m^2) QD on Days 1, 4, 8, and 11. In the expanded part, patients received oral ixazomib (2.0 mg/m^2) QD on Days 1, 4, 8, and 11.

All of 60 patients enrolled in the study (the dose-titration part; 3 each in the 0.24, 0.48, 0.8, 1.2, and 1.68 mg/m^2 groups, 4 in the 2.23 mg/m^2 group, 7 in the 2.0 mg/m^2 group: in the expanded part ;40[23)]) received ixazomib and were included in the safety analysis. Of patients who were enrolled in the dose titration part and treated with ixazomib, 24 patients were evaluated for DLT. The remaining 2 patients (1 each in the 2.0 and 2.23 mg/m^2 groups) did not complete Cycle 1 and did not have DLT.

DLT was evaluated in Cycle 1 of the dose-titration part. During this period, DLT was observed in 2 of 3 patients in the 2.23 mg/m^2 group (Grade 3 rash macular and Grade 4 thrombocytopenia in 1 patient each). Accordingly the maximum tolerated dose (MTD) was determined to be 2 mg/m^2.

The safety analysis revealed deaths of 2 of 60 patients (3.3%) during treatment or within 30 days after the last dose. The causes of death were disease progression (in the expanded part) and cardiovascular disorder (0.8 mg/m^2 group in the dose titration part). A causal relationship to ixazomib was ruled out for both events.

[23)] Six of 40 patients were also included in in the 2.0 mg/m^2 group in the dose titration part.

7.1.3.7 Foreign Phase I study (CTD 5.3.5.2-4, Study C16004 [Ongoing since October 2009 (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with relapsed or refractory MM (target sample size, 36 subjects in the dose titration part, 34 subjects in the expanded part) at 6 centers overseas.

Each treatment cycle consisted of 28 days. Patients received oral ixazomib (0.24, 0.48, 0.8, 1.2, 1.68, 2.23, 2.97, or 3.95 mg/m^2) QD in the dose titration part, and ixazomib (2.97 mg/m^2) QD in the expanded part, both on Days 1, 8, and 15.

All of 60 patients enrolled in the study (in the dose titration part; 3 each in the 0.24, 0.48, 0.80, 1.20, and 2.23 mg/m^2 groups, 4 in the 1.68 mg/m^2 group, 5 in the 3.95 mg/m^2 group, 8 in the 2.97 mg/m^2 group: the expanded part; 31[24)]) received ixazomib, and were included in the safety analysis. Of patients who were enrolled in the dose titration part and treated with the study drug, 29 patients were evaluated for DLT. The remaining 3 patients did not complete Cycle 1 and did not have DLT (2 in the 2.97 mg/m^2 group and 1 in the 3.95 mg/m^2 group).

DLT was evaluated in Cycle 1 of the dose-titration part. During this period, DLT was observed in 1 of 6 patients in the 2.97 mg/m^2 group (Grade 3 nausea/vomiting/diarrhoea in 1 patient) and in 2 of 4 patients in the 3.95 mg/m^2 group (Grade 3 nausea/vomiting/diarrhoea and Grade 3 erythema multiforme in 1 patient each). MTD was determined to be 2.97 mg/m^2.

The safety analysis revealed a death of 1 of 60 patients (1.7%) during treatment or within 30 days after the last dose. The cause of death was disease progression (1 patient in the 2.97 mg/m^2 group in the dose titration part), and its causal relationship to ixazomib was ruled out.

7.1.3.8 Foreign Phase I/II study (CTD 5.3.5.2-5, Study C16005 [Ongoing since November 2010 (data cut-off, March 8, 2013)])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with newly diagnosed MM (target sample size, 12 subjects in Phase I and 46 subjects in Phase II) at 11 centers overseas.

One treatment cycle consisted of 28 days. Patients received oral ixazomib (1.68, 2.23, 2.97, or 3.95 mg/m^2) in Phase I, and oral ixazomib (4.0 mg) QD on Days 1, 8, and 15 in Phase II, in combination with the Ld regimen[14)] in both phases.

All of 65 patients enrolled in the study (Phase I; 3 each in the 1.68, 2.23, and 3.95 mg/m^2 groups, 6 in the 2.97 mg/m^2 group: Phase II; 50) received the study drug and were included in the safety analysis. Of patients who were enrolled in the Phase I and treated with the study drug, 13 patients were evaluated for DLT. The remaining 2 patients did not complete Cycle 1 and did not have DLT (1 patient each in the 1.68 and 2.97 mg/m^2 groups).

DLT was evaluated in Cycle 1 of Phase I. During this period, DLT was observed in 1 of 5 patients in the 2.97 mg/m^2 group (Grade 3 urticaria in 1 patient) and in 3 of 3 patients in the 3.95 mg/m^2 group (Grade 2 nausea/vomiting, Grade 2 neuropathy peripheral/Grade 3 nausea/vomiting/syncope, and Grade 2 dizziness/orthostatic hypotension/Grade 3 nausea/vomiting in 1 patient each). MTD was determined to be 2.97 mg/m^2.

The safety analysis revealed no death in Phase I and deaths of 2 of 50 patients (4.0%) in Phase II during treatment or within 30 days after the last dose. The causes of death were cardio-respiratory arrest and pneumonia respiratory syncytial viral (1 patient each). A causal relationship to the study drug could not be ruled out for pneumonia respiratory syncytial viral (1 patient).

[24)] Three of 31 patients were also included in the 2.97 mg/m^2 group in the dose titration part.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign Phase I study (CTD 5.3.5.2-1, Study C16001 [Ongoing since March 2009 to April 2012])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with advanced solid cancer (target sample size, 101 subjects) at 7 centers overseas.

All of 116 patients enrolled in the study received ixazomib and were included in the safety analysis.

The safety analysis showed that 7 of 116 patients (6.0%) died during treatment or within 30 days after the last dose. The causes of deaths were disease progression (5 patients) and acute renal failure/hypotension and obstructive pneumonia (1 patient each). A causal relationship to ixazomib was ruled out for all of these events.

7.2.1.2 Foreign Phase I study (CTD 5.3.5.2-2, Study C16002 [August 2009 to October 2014])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with relapsed malignant lymphoma (target sample size, 34 subjects) at 7 centers overseas.

Of 31 patients enrolled in the study, 30 patients who received ixazomib were included in the safety analysis.

The safety analysis revealed a death of 1 of the 30 patients (3.3%) during treatment or within 30 days after the last dose. The cause of death was respiratory failure, and its causal relationship to ixazomib was ruled out.

7.2.1.3 Foreign Phase I study (CTD 5.3.5.2-6, Study C16007 [Ongoing since May 2011 (data cut-off, December [redacted], 2013)])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib in patients with relapsed or refractory light chain amyloidosis (target sample size, 50 subjects) at 9 centers overseas.

All of 27 patients enrolled in the study received ixazomib and were included in the safety analysis.

The safety analysis revealed a death of 1 of the 27 patients (3.7%) during treatment or within 30 days after the last dose. The cause of death was cardiac failure congestive, and its causal relationship to ixazomib was ruled out.

7.2.1.4 Foreign Phase I/II study (CTD 5.3.5.2-7, Study C16008 [Ongoing since October 2011 (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety, etc. of ixazomib combined with lenalidomide and DEX[25)] in patients with newly diagnosed MM (target sample size, 58 subjects) at 15 centers overseas.

All of 64 patients enrolled in the study received the study drug and were included in the safety analysis.

The safety analysis revealed a death of 1 of the 64 patients (1.6%) during treatment or within 30 days after the last dose. The cause of death was cardio-respiratory arrest, and its causal relationship to the study drug could not be ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided that the most important data submitted for the evaluation of the efficacy and safety of ixazomib would be of the global Phase III study in patients with relapsed or refractory MM (Study C16010). Therefore, the review focused on Study C16010. The efficacy in Japanese patients was evaluated based on the consistency of data between the Japanese population and the entire population

25) Oral lenalidomide (25 mg) on Day 1 to Day 14 and oral DEX (20 mg in Cycle 1 to Cycle 8, 10 mg in Cycle 9 to Cycle 16) on Days 1, 2, 4, 5, 8, 9, 11, and 12

in Study C16010, according to "Basic Principles on Global Clinical Trials (PFSB/ELD Notification No. 0928010 dated September 28, 2007)" and "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative notice dated September 5, 2012), and others.

7.R.2 Efficacy

Based on the following review, PMDA concluded that the ixazomib is effective in patients with relapsed or refractory MM.

7.R.2.1 Control group

The applicant's justification for setting the control group in Study C16010:

In 2012 when Study C16010 began targeting patients with relapsed or refractory MM, the clinical practice guideline developed by IMWG (*Leukemia*. 2009;23:1716-30) recommended the LD regimen[26)] to treat relapsed or refractory MM, based on the results of a foreign clinical study (*New Engl J Med*. 2007;357:2123-32). Meanwhile, another foreign clinical study conducted in patients with newly diagnosed MM indicated a trend toward prolonged OS and infrequent adverse events under the Ld regimen[14)] as compared with the LD regimen (*Lancet Oncol*. 2010;11:29-37). Therefore, the placebo/Ld was selected as the control in Study C16010.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the reason for selecting PFS as the primary endpoint for Study C16010:

MM is a relapsing and refractory disease that cannot be cured by conventional treatments. It is known that the duration of treatment efficacy in MM decreases with increasing the number of prior regimens (*Mayo Clin Proc*. 2004;79:867-74). Treatment of patients with relapsed or refractory MM is aimed at life prolongation. However, better response rate and prolonged PFS are expected to lead to improved symptoms, delayed disease progression, and an increase in time to the next treatment (*Leukemia*. 2006;20:1467-73), PFS was selected as the primary endpoint in Study C16010.

PMDA's view:

The applicant's explanation is generally acceptable. However, OS also is important in evaluating the treatment effect for relapsed or refractory MM, a disease with no standard treatment established. Therefore, efficacy of ixazomib was evaluated focused on PFS assessed by IRC according to IMWG criteria, the parameter set as the primary endpoint, but OS also was evaluated.

7.R.2.3 Results of efficacy evaluation

Superiority of the ixazomib/Ld to the placebo/Ld in PFS assessed by IRC according to IMWG criteria, the primary endpoint of Study C16010, was evaluated [see Section "7.1.2.1 Global Phase III study"]. Results of PFS in the per-protocol population, assessed by IRC according to IMWG criteria as the sensitivity analysis, are shown in Table 20.

Table 20. Results of PFS analysis (per-protocol population, IRC assessment, data cut-off October 30, 2014)

	Ixazomib/Ld	Placebo/Ld
Number of patients	348	353
Number of death or aggravation (%)	123 (35.3)	156 (44.2)
Median (months)	20.6	14.7
[95% CI]	[17.0, NE]	[12.9, 17.6]
Hazard ratio [95% CI][*1]	0.71 [0.56, 0.91]	
P value (two-sided)[*2]	0.005	

[*1] Stratified Cox proportional hazard model with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (with or without), and ISS stage at screening (1 or 2, 3) as the stratification factors

[*2] Stratified log-rank test with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (with or without), and ISS stage at screening (1 or 2, 3) as the stratification factors

[26)] The regimen of oral lenalidomide (25 mg) on Day 1 to Day 21 and oral DEX (40 mg) on Day 1 to Day 4, Day 9 to Day 12, and Day 17 to Day 20 of Cycle 1 to Cycle 4 and on Day 1 to Day 4 on Cycle 5 onward. Each treatment cycle consisted of 28 days.

Table 21 shows the results of the second interim analysis (data cut-off, July 12, 2015) of OS, a secondary endpoint, and Figure 3 shows Kaplan-Meier curves of OS.

Table 21. OS in the second interim analysis (ITT population, data cut-off July 12, 2015)

	Ixazomib/Ld	Placebo/Ld
Number of patients	360	362
Number of death (%)	81 (22.5)	90 (24.9)
Median [95% CI] (months)	NE [NE, NE]	NE [30.9, NE]
Hazard ratio [95% CI][*1]	0.87 [0.64, 1.18]	
P value (two-sided)[*2]	0.359	

[*1] Stratified Cox proportional hazard model with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (with or without), and ISS stage at screening (1 or 2, 3) as the stratification factors

[*2] Stratified log-rank test with the number of prior regimens (1, 2 or 3), prior regimen with proteasome inhibitor (with or without), and ISS stage at screening (1 or 2, 3) as the stratification factors. Significance level of 0.00031 (two-sided).

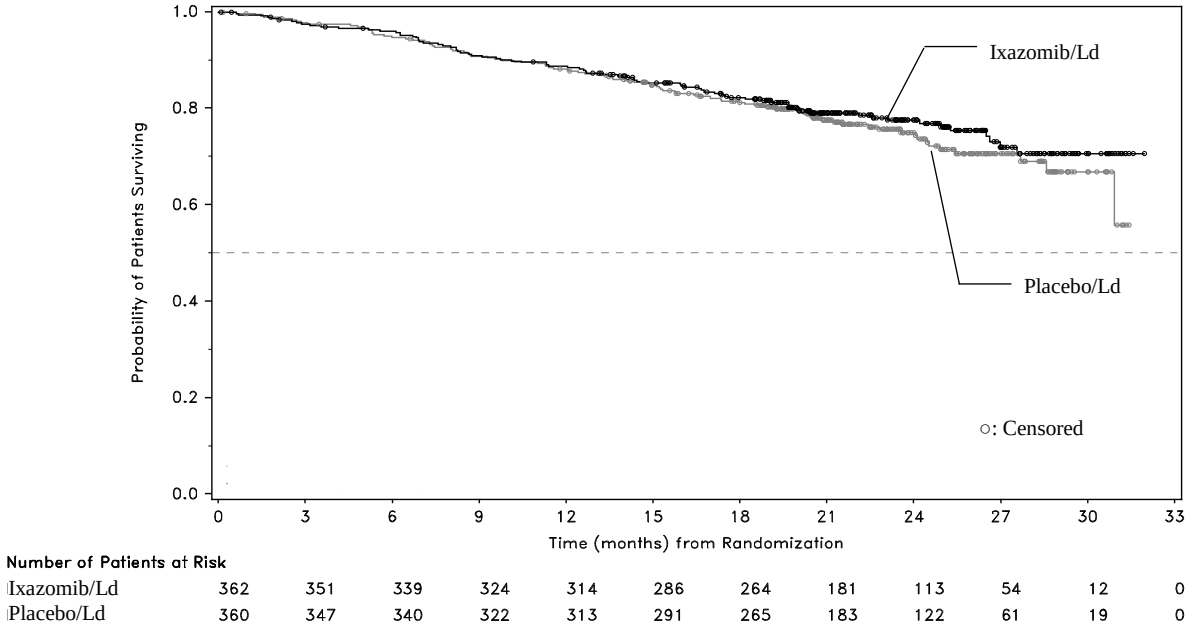

Figure 3. Kaplan-Meier curves of OS in the second interim analysis (ITT population, data cut-off July 12, 2015)

PMDA's view:
Results of Study C16010 demonstrated the superiority of the ixazomib/Ld group to the placebo/Ld group in the primary endpoint, i.e., PFS assessed by IRC according to IMWG criteria, and suggested that the observed PFS-prolonging effect is clinically significant. No tendency of OS, a secondary endpoint to decrease in the ixazomib/Ld group as compared to the placebo/Ld group.

Based on the above, PMDA concluded that ixazomib is effective in patients with relapsed or refractory MM.

7.R.2.4 Efficacy in Japanese patients

Table 22 shows the results of PFS in the Japanese population of Study C16010, assessed by IRC according to IMWG criteria in the second interim analysis.[27)] Figure 4 shows Kaplan-Meier curves of PFS. The hazard ratio of PFS in the entire population of Study C16010, assessed by IRC according to IMWG criteria in the second interim analysis, was 0.818.

[27)] The first interim analysis of Study C16010 was conducted at 26 months after the start of enrollment, which was equivalent to 11 months after the start of enrollment in the Japanese subgroup. The number of events in the Japanese population at the time point would be not sufficient enough to ensure consistency in PFS between the Japanese population and the entire population. Therefore, efficacy evaluation in the Japanese population was decided to be conducted at the second interim analysis.

Table 22. Results of PFS analysis in Japanese population (ITT population, IRC assessment, data cut-off July 12, 2015)

	Ixazomib/Ld	Placebo/Ld
Number of patients	20	21
Number of death or aggravation (%)	7 (35.0)	8 (38.1)
Median [95% CI] (months)	17.0 [10.2, NE]	18.7 [7.4, 18.8]
Hazard ratio[*1] [95% CI]	1.32 [0.44, 3.95]	
P value (two-sided)[*2]	0.614	

[*1] Non-stratified Cox proportional hazard model, [*2] Non-stratified log-rank test

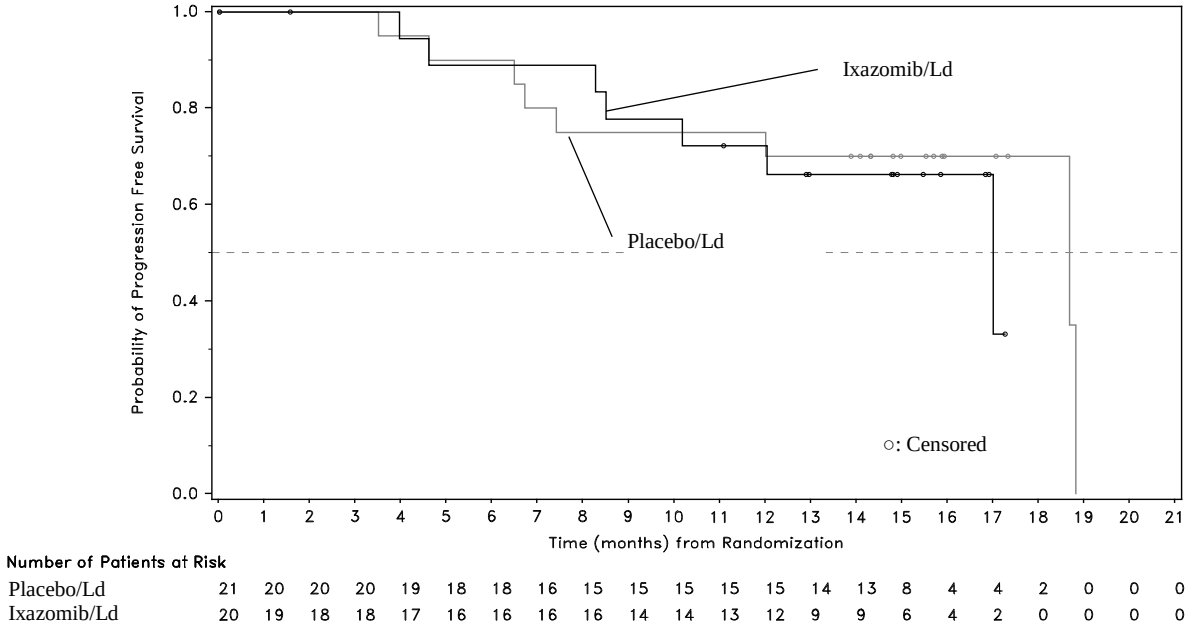

Figure 4. Kaplan-Meier curves of PFS in Japanese population (ITT population, IRC assessment, data cut-off July 12, 2015)

Table 23 shows the results of other secondary endpoints (response rate and percentage of patients with VGPR or better) other than OS in the entire population and in the Japanese population. No OS-related event was observed in the Japanese population, either in the ixazomib/Ld group or in the placebo/Ld group.

Table 23. Best overall response (ITT population, IRC assessment)

Best overall response	Entire population[*1]		Japanese population[*2]	
	Ixazomib/Ld	Placebo/Ld	Ixazomib/Ld	Placebo/Ld
Number of patients	360	362	20	21
Stringent complete response (sCR)	9 (2.5)	3 (0.8)	0	2 (9.5)
Complete response (CR)	33 (9.2)	21 (5.8)	6 (30.0)	5 (23.8)
Very good partial response (VGPR)	131 (36.4)	117 (32.3)	5 (25.0)	5 (23.8)
Partial response (PR)	109 (30.3)	118 (32.6)	4 (20.0)	7 (33.3)
Stable disease (SD)	40 (11.1)	59 (16.3)	2 (10.0)	1 (4.8)
Progressive disease (PD)	17 (4.7)	20 (5.5)	0	0
Not evaluable (NE)	21 (5.8)	24 (6.6)	3 (15.0)	1 (4.8)
Response rate (rate of sCR, CR, VGPR, or PR) [95% CI] (%)	78.3 [73.7, 82.5]	71.5 [66.6, 76.1]	75.0 [50.9, 91.3]	90.5 [69.6, 98.8]
Odds ratio	1.44 [1.03, 2.03]		0.32 [0.05, 1.86]	
Percentage of patients with VGPR or better (sCR, CR, or VGPR) [95% CI] (%)	48.1 [42.8, 53.4]	39.0 [33.9, 44.2]	55.0 [31.5, 76.9]	57.1 [34.0, 78.2]
Odds ratio	1.45 [1.08, 1.95]		0.92 [0.27, 3.15]	

[*1] Data cut-off October 30, 2014, [*2] Data cut-off July 12, 2015

Because Study C16010 failed to demonstrate consistency between the Japanese population and the entire population in PFS and other efficacy parameters, PMDA asked the applicant to explain the efficacy of ixazomib in Japanese patients with relapsed or refractory MM.

The applicant's explanation:
In the Japanese population of Study C16010, (a) the hazard ratio of PFS was >1, and (b) the point estimate of the odds ratio of the response rate was <1. Whether the imbalance in prognostic factors caused these results was investigated as described below. The results thus obtained suggested that the imbalance in poor prognostic factors was unlikely to have caused the above effects. However, that in the Japanese population of Study C16010, both the hazard ratio of PFS and the odds ratio of response rate in ixazomib/Ld placebo/Ld had a wide 95% CI, which overlapped the 95% CI of the hazard ratio of PFS and the odds ratio of response rate in the entire population. The data do not strongly deny the consistency between the Japanese population and the entire population.

- Using the results of PFS in the non-Japanese population in the first interim analysis of Study C16010 and the results of PFS in the Japanese population in the second interim analysis, a sample population showing the similar distribution of prognostic factors as that in the Japanese population was extracted from the non-Japanese population of Study C16010 by 1000 stratified random sampling based on the poor prognostic factor selected by stepwise variable selection (cytogenetic risk [high risk, other than high risk]) and on international staging system (ISS) stage (1 or 2, 3) at registration, and the distribution of the hazard ratio of PFS was obtained from this population. When the size of the sample population was matched to that of the Japanese population, the median [2.5 percentile, 97.5 percentile] hazard ratio distribution was 0.75 [0.26, 1.90], with 11.0% of the population showing a PFS hazard ratio of not less than 1.32, the ratio observed in the Japanese population. When the size of the sample population was the maximum size extractable from the non-Japanese population, the median [2.5 percentile, 97.5 percentile] hazard ratio distribution was 0.72 [0.54, 0.95], which was not significantly different from the hazard ratio in the entire population (0.74).
- Using the results of response rate in the non-Japanese population in the first interim analysis of Study C16010 and the results of response rate in the Japanese population in the second interim analysis, a sample population showing the similar distribution of prognostic factors as that in the Japanese population was extracted from the non-Japanese population of Study C16010 by 1000 stratified random sampling, based on the poor prognostic factors selected by stepwise variable selection (refractory to prior regimen or not, Eastern Cooperative Oncology Group [ECOG] performance status [0, 1 or 2], age), and the distribution of the odds ratio of response rate was obtained from this population. When the size of the sample population was matched to that of the Japanese population, the median [2.5 percentile, 97.5 percentile] of the odds ratio distribution was 1.33 [0.38, 5.74], with approximately 2% of the population showing an odds ratio in response rate of not more than 0.32, the ratio observed in the Japanese population. When a sample population was extracted at the maximum size extractable from the non-Japanese population by combining strata with a small sample size, the median [2.5 percentile, 97.5 percentile] of the odds ratio distribution was 1.15 [0.69, 1.98], which was lower than the odds ratio in the entire population (1.44) but >1.

PMDA's view:
Results of PFS, etc. in Study C16010 did not demonstrate the consistency of the efficacy of ixazomib between the Japanese population and the entire population, failing to clearly suggest the efficacy of ixazomib in the Japanese population. Therefore, it cannot be affirmatively concluded that ixazomib is effective in Japanese patients.

Clinical benefits of ixazomib in Japanese patients with relapsed or refractory MM should be discussed in light of the results of Study C16010 overall as described in Section "7.R.4 Clinical positioning."

7.R.3 Safety (for adverse events, see Section "7.3 Adverse events, etc. observed in clinical studies")

As a results of the review detailed in the following subsections, PMDA concluded that adverse events requiring particular attention in treatment with ixazomib are thrombocytopenia, gastrointestinal disorders, peripheral nerve disorder, skin disorder, infection, and posterior reversible encephalopathy syndrome, and that a caution should be exercised against these possible adverse events in using ixazomib.

PMDA also concluded that although attention should be paid to the mentioned adverse events during treatment, ixazomib should be well tolerated as long as patients are followed by physicians with

adequate knowledge and experience in the treatment of hematopoietic malignancy through monitoring and control of adverse events and any other appropriate actions. Because of the extremely limited experience in the use of ixazomib in Japanese patients, post-marketing safety data should be collected [see Section "7.R.6 Dosage and administration"].

7.R.3.1 Safety profile of ixazomib

The applicant explained the safety profile of ixazomib, based on the safety data obtained from Study C16010 (data cut-off, July 12, 2015), as follows:
Table 24 shows the outline of safety in Study C16010.

Table 24. Outline of safety profile (Study C16010)

	Number of patients (%)	
	Ixazomib/Ld N = 361	Placebo/Ld N = 359
All adverse events	355 (98.3)	357 (99.4)
Grade ≥3 adverse events	267 (74.0)	247 (68.8)
Adverse events resulting in death	15 (4.2)	23 (6.4)
Serious adverse events	168 (46.5)	177 (49.3)
Adverse events leading to treatment discontinuation*	91 (25.2)	73 (20.3)
Adverse events leading to treatment interruption*	192 (53.2)	130 (36.2)
Adverse events leading to dose reduction*	203 (56.2)	181 (50.4)

* Any ≥1 of 3 drugs (ixazomib or placebo, lenalidomide, and DEX)

All Grade adverse events with ≥10% higher incidence in the ixazomib/Ld group than in the placebo/Ld group were thrombocytopenia (86 of 361 patients [23.8%] in the ixazomib/Ld group, 41 of 359 patients [11.4%] in the placebo/Ld group) and vomiting (84 of 361 patients [23.3%], 42 of 359 patients [11.7%]). Grade ≥3 adverse event with ≥5% higher incidence in the ixazomib/Ld group than in the placebo/Ld group was thrombocytopenia (55 of 361 patients [15.2%], 22 of 359 patients [6.1%]). Adverse events leading to treatment interruption with ≥2% higher incidence in the ixazomib/Ld group than in the placebo/Ld group were thrombocytopenia (31 of 361 patients [8.6%], 9 of 359 patients [2.5%]), diarrhoea (22 of 361 patients [6.1%], 7 of 359 patients [1.9%]), neutropenia (18 of 361 patients [5.0%], 6 of 359 patients [1.7%]), peripheral sensory neuropathy (14 of 361 patients [3.9%], 2 of 359 patients [0.6%]), rash maculo-papular (12 of 361 patients [3.3%], 4 of 359 patients [1.1%]), and nausea (11 of 361 patients [3.0%], 3 of 359 patients [0.8%]). Adverse events leading to dose reduction with ≥2% higher incidence in the ixazomib/Ld group than in the placebo/Ld group were thrombocytopenia (26 of 361 patients [7.2%], 10 of 359 patients [2.8%]), diarrhoea (18 of 361 patients [5.0%], 10 of 359 patients [2.8%]), and peripheral sensory neuropathy (17 of 361 patients [4.7%], 8 of 359 patients [2.2%]). There were no serious adverse events or adverse events leading to treatment discontinuation with ≥2% higher incidence in the ixazomib/Ld group than in the placebo/Ld group.

PMDA's view:
Adverse events with a higher incidence in the ixazomib/Ld group than in the placebo/Ld group in Study C16010 require a caution as ixazomib-induced events. Data of relevant events should be provided to healthcare professionals in an appropriate manner.

7.R.3.2 Difference in safety profile between Japanese and non-Japanese patients

Based on the safety data obtained in Study C16010, the applicant explained the difference in the safety profile of ixazomib in Japanese patients and in non-Japanese patients as follows:
Table 25 shows the outline of the safety profile in Japanese and non-Japanese patients in Study C16010.

Table 25. Outline of the difference in safety profile between Japanese and non-Japanese patients (Study C16010)

	Number of patients (%)			
	Japanese patients		Non-Japanese patients	
	Ixazomib/Ld N = 20	Placebo/Ld N = 21	Ixazomib/Ld N = 341	Placebo/Ld N = 338
All adverse events	20 (100)	21 (100)	335 (98.2)	336 (99.4)
Grade ≥3 adverse events	15 (75.0)	18 (85.7)	252 (73.9)	229 (67.8)
Adverse events resulting in death	0	0	15 (4.4)	23 (6.8)
Serious adverse events	5 (25.0)	6 (28.6)	163 (47.8)	171 (50.6)
Adverse events leading to treatment discontinuation*	3 (15.0)	3 (14.3)	88 (25.8)	70 (20.7)
Adverse events leading to treatment interruption*	11 (55.0)	8 (38.1)	181 (53.1)	122 (36.1)
Adverse events leading to dose reduction*	12 (60.0)	12 (57.1)	191 (56.0)	169 (50.0)

* Any ≥1 of 3 drugs (ixazomib or placebo, lenalidomide, and DEX)

Adverse events with ≥20% higher incidence in Japanese patients than in non-Japanese patients in the ixazomib/Ld group of Study C16010 were vomiting (9 of 20 patients [45.0%] in Japanese patients, 75 of 341 patients [22.0%] in non-Japanese patients), nasopharyngitis (11 of 20 patients [55.0%], 70 of 341 patients [20.5%]), malaise (9 of 20 patients [45.0%], 8 of 341 patients [2.3%]), dysgeusia (7 of 20 patients [35.0%], 26 of 341 patients [7.6%]), rash maculo-papular (7 of 20 patients [35.0%], 25 of 341 patients [7.3%]), and dental caries (5 of 20 patients [25.0%], 3 of 341 patients [0.9%]). Grade ≥3 adverse events with ≥10% higher incidence in Japanese patients than in non-Japanese patients were diarrhoea (4 of 20 patients [20.0%], 19 of 341 patients [5.6%]) and rash maculo-papular (3 of 20 patients [15.0%], 4 of 341 patients [1.2%]). The adverse event leading to treatment interruption with ≥10% higher incidence in Japanese patients than in non-Japanese patients was rash maculo-papular (5 of 20 patients [25.0%], 7 of 341 patients [2.1%]). Adverse events leading to dose reduction with ≥10% higher incidence in Japanese patients than in non-Japanese patients were rash maculo-papular (4 of 20 patients [20.0%], 6 of 341 patients [1.8%]), nausea (3 of 20 patients [15.0%], 6 of 341 patients [1.8%]), and diarrhoea (3 of 20 patients [15.0%], 15 of 341 patients [4.4%]). There were no adverse events resulting in death with a higher incidence in Japanese patients than in non-Japanese patients. Also, there were no serious adverse events or adverse events leading to treatment discontinuation, with ≥10% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:
Because of the limited number of Japanese patients studied, it is practically impossible to derive clear conclusion on the difference in safety profile between Japanese and non-Japanese patients based on the results of Study C16010. However, attention should be paid to Grade ≥3 adverse events with a higher incidence in Japanese patients than in non-Japanese patients. Data on the occurrence of these events should be appropriately provided to healthcare professionals in written materials, etc. Also, because of limited information on the safety of ixazomib in Japanese patients, relevant data should be further collected after the market launch, and new findings should be appropriately provided to healthcare professionals.

In the following sections, PMDA reviewed the safety data of ixazomib based mainly from Study C16010, focusing on Grade ≥3 adverse events with a higher incidence in the ixazomib/Ld group than in the placebo/Ld group and on adverse events leading to treatment interruption.

7.R.3.3 Bone marrow depression

The applicant's explanation about the incidences of bone marrow depression associated with ixazomib:
As adverse events related to bone marrow depression, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) corresponding to "Haematopoietic cytopenias (broad)" in the standard MedDRA queries (SMQ) (MedDRA ver. 16.0) were tabulated.

Table 26 shows the incidences of bone marrow depression in Study C16010.

Table 26. Incidences of bone marrow depression (Study C16010)

MedDRA PT (MedDRA ver. 16.0)	Number of patients (%) Study C16010			
	Ixazomib/Ld N = 361		Placebo/Ld N = 359	
	All grades	Grade ≥3	All grades	Grade ≥3
Bone marrow depression	201 (55.7)	137 (38.0)	183 (51.0)	130 (36.2)
Neutropenia	103 (28.5)	74 (20.5)	92 (25.6)	71 (19.8)
Anaemia	103 (28.5)	34 (9.4)	98 (27.3)	48 (13.4)
Thrombocytopenia	86 (23.8)	55 (15.2)	41 (11.4)	22 (6.1)
Platelet count decreased	30 (8.3)	15 (4.2)	19 (5.3)	11 (3.1)
Leukopenia	24 (6.6)	16 (4.4)	18 (5.0)	6 (1.7)
Neutrophil count decreased	22 (6.1)	12 (3.3)	23 (6.4)	17 (4.7)
White blood cell count decreased	9 (2.5)	1 (0.3)	12 (3.3)	3 (0.8)
Lymphocyte count decreased	8 (2.2)	5 (1.4)	10 (2.8)	7 (1.9)
Lymphopenia	5 (1.4)	2 (0.6)	4 (1.1)	2 (0.6)
Pancytopenia	6 (1.7)	3 (0.8)	4 (1.1)	2 (0.6)
Haemoglobin decreased	4 (1.1)	[redacted]	4 (1.1)	[redacted]
Febrile neutropenia	2 (0.6)	2 (0.6)	8 (2.2)	8 (2.2)
Anaemia macrocytic	2 (0.6)	0	1 (0.3)	0
Myelodysplastic syndrome	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Granulocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Microcytic anaemia				
Eosinophil count decreased				
Monocyte count decreased				

There was no fatal bone marrow depression in Study C16010. Serious bone marrow depression was observed in [redacted] patients in the [redacted] group ([redacted]%; thrombocytopenia in 5 patients, anaemia in 3 patients, neutropenia, platelet count decreased, pancytopenia, and febrile neutropenia in 2 patients each, myelodysplastic syndrome in [redacted] patients [some patients had >1 adverse event]) and in [redacted] patients in the [redacted] group ([redacted]%; anaemia and febrile neutropenia in 8 patients each, thrombocytopenia in 5 patients, neutropenia in 2 patients, platelet count decreased, leukopenia, and pancytopenia in [redacted] patients each [some patients had >1 adverse event]). A causal relationship to the study drug could not be ruled out for thrombocytopenia (4 patients), and anaemia, neutropenia, platelet count decreased, pancytopenia, and febrile neutropenia (2 patients each) in the [redacted] group; and anaemia, febrile neutropenia, and thrombocytopenia (5 patients each), neutropenia (2 patients), and platelet count decreased, leukopenia, and pancytopenia ([redacted] patients each) in the [redacted] group. Bone marrow depression led to discontinuation of the study drug in 11 of 361 patients (3.0%) in the ixazomib/Ld group and in 12 of 359 patients (3.3%) in the placebo/Ld group, to interruption of the study drug in 51 of 361 patients (14.1%) in the ixazomib/Ld group and in 26 of 359 patients (7.2%) in the placebo/Ld group, and to dose reduction of the study drug in 57 of 361 patients (15.8%) in the ixazomib/Ld group and in 42 of 359 patients (11.7%) in the placebo/Ld group.

PMDA's view:
In Study C16010, the incidences of all grades and Grade ≥3 bone marrow depression were comparable between the ixazomib/Ld group and the placebo/Ld group. In terms of thrombocytopenia, the incidences that of Grade ≥3 and that leading to treatment suspension, or dose reduction[28)] were higher in the ixazomib/Ld group than in the placebo/Ld group. This indicates the need for attention to thrombocytopenia during treatment with ixazomib. Therefore, data on the occurrences of relevant events in clinical studies should be communicated to healthcare professionals. Healthcare professionals should also be advised in the package insert, etc. to monitor platelet count in during the use of ixazomib and to take appropriate measures, such as treatment suspension, in case any abnormality.

7.R.3.4 Gastrointestinal disorders

The applicant's explanation about the incidences of gastrointestinal disorders associated with ixazomib:

[28)] Thrombocytopenia led to interruption of the study drug in 31 of 361 patients (8.6%) in the ixazomib/Ld group and in 9 of 359 patients (2.5%) in the placebo/Ld group, and to dose reduction of the study drug in 26 of 361 patients (7.2%) in the ixazomib/Ld group and in 10 of 359 patients (2.8%) in the placebo/Ld group.

As adverse events related to gastrointestinal disorders, MedDRA PTs corresponding to "Gastrointestinal disorders" in MedDRA system organ class (SOC) (MedDRA ver. 16.0) were tabulated.

Table 27 shows the incidences of gastrointestinal disorders in Study C16010.

Table 27. Gastrointestinal disorders with an incidence of ≥5% in either group (Study C16010)

MedDRA PT (MedDRA ver. 16.0)	Number of patients (%)			
	Ixazomib/Ld N = 361		Placebo/Ld N = 359	
	All grades	Grade ≥3	All grades	Grade ≥3
Gastrointestinal disorders	268 (74.2)	39 (10.8)	245 (68.2)	16 (4.5)
Diarrhoea	164 (45.4)	23 (6.4)	139 (38.7)	9 (2.5)
Constipation	126 (34.9)	1 (0.3)	94 (26.2)	1 (0.3)
Nausea	104 (28.8)	[redacted]	79 (22.0)	[redacted]
Vomiting	84 (23.3)	4 (1.1)	42 (11.7)	2 (0.6)
Abdominal pain	33 (9.1)	[redacted]	28 (7.8)	[redacted]
Dyspepsia	29 (8.0)	0	27 (7.5)	0
Abdominal pain upper	24 (6.6)	[redacted]	16 (4.5)	[redacted]
Dry mouth	15 (4.2)	0	25 (7.0)	0

There were no fatal gastrointestinal disorders in Study C16010. Serious gastrointestinal disorders were observed in [redacted] patients in the [redacted] group ([redacted]%; diarrhoea in 9 patients, nausea, vomiting, dyspepsia, inguinal hernia, and ileus paralytic in [redacted] patients each, constipation, abdominal pain, abdominal pain upper, abdominal pain lower, rectal haemorrhage, colitis, colitis ischaemic, gastrooesophageal reflux disease, obstructive femoral hernia, ileus, intestinal obstruction, oesophageal achalasia, pancreatitis, and small intestinal obstruction in [redacted] patients each [some patients had >1 adverse event]), and in [redacted] patients in the [redacted] group ([redacted]%; diarrhoea in 2 patients, constipation, haematochezia, inguinal hernia, colitis, melaena, oesophageal ulcer, and pancreatitis acute in [redacted] patients each). A causal relationship to the study drug could not be ruled out for diarrhoea (7 patients), vomiting ([redacted] patients), nausea, dyspepsia, ileus paralytic, abdominal pain, abdominal pain upper, obstructive femoral hernia, colitis, gastrooesophageal reflux disease, and oesophageal achalasia ([redacted] patients each) in the [redacted] group, and for diarrhoea and constipation ([redacted] patients each) in the [redacted] group. Gastrointestinal disorders led to discontinuation of the study drug in 7 of 361 patients (1.9%) in the ixazomib/Ld group and 3 of 359 patients (0.8%) in the placebo/Ld group, interruption of the study drug in 43 of 361 patients (11.9%) in the ixazomib/Ld group and 12 of 359 patients (3.3%), in the placebo/Ld group, and dose reduction of the study drug in 44 of 361 patients (12.2%) in the ixazomib/Ld group and 24 of 359 patients (6.7%) in the placebo/Ld group.

PMDA's view:
In Study C16010, the incidences of Grade ≥3 gastrointestinal disorders and serious gastrointestinal disorders were higher in the ixazomib/Ld group than in the placebo/Ld group, and there were gastrointestinal disorders with higher incidence in Japanese patients than in non-Japanese patients. Therefore, treatment with ixazomib requires close attention to gastrointestinal disorders. Data on the occurrences of relevant events in clinical studies should be provided to healthcare professionals through the package insert, etc.

7.R.3.5 Peripheral nerve disorders

The applicant's explanation about peripheral nerve disorders associated with ixazomib:
As peripheral nerve disorders, MedDRA PTs corresponding to "Peripheral neuropathies NEC" in MedDRA high level term (HLT) (MedDRA ver. 16.0) were tabulated.

Table 28 shows the incidences of peripheral nerve disorders in Study C16010.

Table 28. Incidences of peripheral nerve disorders (Study C16010)

MedDRA PT (MedDRA ver. 16.0)	Number of patients (%)			
	Ixazomib/Ld N = 361		Placebo/Ld N = 359	
	All grades	Grade ≥3	All grades	Grade ≥3
Peripheral nerve disorders	98 (27.1)	9 (2.5)	78 (21.7)	6 (1.7)
Peripheral sensory neuropathy	69 (19.1)	6 (1.7)	53 (14.8)	4 (1.1)
Neuropathy peripheral	34 (9.4)	2 (0.6)	25 (7.0)	1 (0.3)
Peripheral motor neuropathy	1 (0.3)	[redacted]	2 (0.6)	[redacted]
Peripheral sensorimotor neuropathy	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Neuritis	[redacted]	0	[redacted]	0

No serious peripheral nerve disorders were observed in Study C16010. Peripheral nerve disorders led to discontinuation of the study drug in 9 of 361 patients (2.5%) in the ixazomib/Ld group and in 2 of 359 patients (0.6%) in the placebo/Ld group, to interruption of the study drug in 19 of 361 patients (5.3%) in the ixazomib/Ld group and in 5 of 359 patients (1.4%) in the placebo/Ld group, and to dose reduction of the study drug in 21 of 361 patients (5.8%) in the ixazomib/Ld group and in 14 of 359 patients (3.9%) in the placebo/Ld group.

In clinical studies other than Study C16010,[29)] no fatal peripheral nerve disorders were observed, whereas serious peripheral nerve disorders were observed in 3 patients (neuropathy peripheral [2 patients], peripheral sensory neuropathy [1 patient]), and a causal relationship to ixazomib could not be ruled out for all events.

PMDA's view:
In Study C16010, the incidences of peripheral nerve disorders that led to discontinuation, interruption, or dose reduction, of the study drug were higher in the ixazomib/Ld group than in the placebo/Ld group. Therefore, treatment with ixazomib requires close attention to peripheral nerve disorders. Data on the occurrences of relevant events in clinical studies should be communicated to healthcare professionals in appropriate manner through the package insert, etc., along with precautionary advice on appropriate measures, such as discontinuation, interruption, and dose reduction of ixazomib to be taken in case of peripheral nerve disorder.

7.R.3.6 Skin disorders

The applicant's explanation about the incidences of skin disorders associated with ixazomib:
Adverse events related to skin disorder, MedDRA PTs corresponding to "Skin and subcutaneous tissue disorders" in MedDRA SOC (MedDRA ver. 16.0) were tabulated.

Table 29 shows the incidences of skin disorders in Study C16010. In Study C16010, use of corticosteroid was allowed if rash developed. It was recommended to consider prophylactic use of skin softening cream.

[29)] Japanese Phase I study (Study TB-MC010034), foreign Phase I studies (Studies C16003, C16004, C16007, C16009, C16013, C16015, and C16018), foreign Phase I/II studies (Studies C16005, C16006 [concomitant use of ixazomib, melphalan, and prednisone in patients with MM], and C16008), foreign Phase II study (Studies C16017 [in patients with follicular lymphoma] and C16020 [concomitant use of ixazomib, cyclophosphamide, and DEX in patients with MM]), and foreign Phase III study (Study C16011 [in patients with light chain amyloidosis])

Table 29. Skin disorders with an incidence of ≥2% in either group (Study C16010)

MedDRA PT (MedDRA ver. 16.0)	Number of patients (%)			
	Ixazomib/Ld N = 361		Placebo/Ld N = 359	
	All grades	Grade ≥3	All grades	Grade ≥3
Skin disorders	185 (51.2)	22 (6.1)	140 (39.0)	7 (1.9)
Pruritus	38 (10.5)	[redacted]	25 (7.0)	[redacted]
Rash maculo-papular	32 (8.9)	7 (1.9)	14 (3.9)	3 (0.8)
Rash macular	24 (6.6)	1 (0.3)	25 (7.0)	3 (0.8)
Erythema	18 (5.0)	0	10 (2.8)	0
Rash	16 (4.4)	[redacted]	7 (1.9)	[redacted]
Rash papular	12 (3.3)		3 (0.8)	
Hyperhidrosis	11 (3.0)		18 (5.0)	
Dry skin	11 (3.0)	0	12 (3.3)	0
Skin ulcer	10 (2.8)	[redacted]	4 (1.1)	[redacted]
Rash erythematous	10 (2.8)		2 (0.6)	
Night sweats	6 (1.7)	0	12 (3.3)	0
Alopecia	4 (1.1)	0	9 (2.5)	0

No fatal skin disorders occurred in Study C16010. Serious skin disorders were observed in [redacted] patients in the [redacted] group ([redacted]%; rash, cutaneous vasculitis, and psoriasis in [redacted] patients each) and in [redacted] patients in the [redacted] group ([redacted]%, rash macular in [redacted] patients). A causal relationship to the study drug could not be ruled out for rash, cutaneous vasculitis, and psoriasis ([redacted] patients each) in the [redacted] group. Skin disorders led to discontinuation of the study drug in 5 of 361 patients (1.4%) in the ixazomib/Ld group and in 2 of 359 patients (0.6%) in the placebo/Ld group, to interruption of the study drug in 41 of 361 patients (11.4%) in the ixazomib/Ld group and in 10 of 359 patients (2.8%) in the placebo/Ld group, and to dose reduction of the study drug in 39 of 361 patients (10.8%) in the ixazomib/Ld group and in 17 of 359 patients (4.7%) in the placebo/Ld group.

In clinical studies other than Study C16010,[29)] no fatal skin disorders were reported, whereas serious skin disorders were observed in 11 patients (Stevens-Johnson syndrome [2 patients], rash generalised, erythema multiforme, rash morbilliform, rash maculo-papular, erythema, rash macular, interstitial granulomatous dermatitis, acute febrile neutrophilic dermatosis, and dermatitis [1 patient each]). A causal relationship to ixazomib could not be ruled out for these events except rash morbilliform and erythema (1 patient each).

PMDA's view:
In Study C16010, the incidences of all Grade and Grade ≥3 skin disorders were higher in the ixazomib/Ld group than in the placebo/Ld group. Also, there were skin disorders with a higher incidence in the Japanese patients than in the non-Japanese patients. In addition, serious skin disorders such as Stevens-Johnson syndrome with a suspected causal relationship to ixazomib were observed also in clinical studies other than Study C16010. In light of these observations, treatment with ixazomib requires close attention to skin disorders. Therefore, the occurrences of relevant events in clinical studies should be communicated to healthcare professionals through the package insert, along with precautionary advice on appropriate measures, such as discontinuation, interruption, and dose reduction of ixazomib to be taken in case of skin disorder. Concrete measures taken for rash in clinical studies should be appropriately communicated to healthcare professionals, using written materials, etc.

7.R.3.7 Infection

The applicant's explanation about the incidences of infection associated with ixazomib:
As adverse events related to infection, MedDRA PTs corresponding to "Infections and infestations" in MedDRA SOC (MedDRA ver. 16.0) were tabulated.

Table 30 shows the incidences of infection in Study C16010.

Table 30. Infection with an incidence of ≥5% in either group (Study C16010)

MedDRA PT (MedDRA ver. 16.0)	Number of patients (%)			
	Ixazomib/Ld N = 361		Placebo/Ld N = 359	
	All grades	Grade ≥3	All grades	Grade ≥3
Infection	276 (76.5)	83 (23.0)	266 (74.1)	90 (25.1)
Upper respiratory tract infection	83 (23.0)	2 (0.6)	70 (19.5)	3 (0.8)
Nasopharyngitis	81 (22.4)	0	73 (20.3)	0
Bronchitis	60 (16.6)	1 (0.3)	51 (14.2)	7 (1.9)
Pneumonia	41 (11.4)	29 (8.0)	44 (12.3)	31 (8.6)
Urinary tract infection	30 (8.3)	3 (0.8)	34 (9.5)	6 (1.7)
Influenza	26 (7.2)	6 (1.7)	23 (6.4)	3 (0.8)
Respiratory tract infection	20 (5.5)	4 (1.1)	28 (7.8)	5 (1.4)
Gastroenteritis	20 (5.5)	[redacted]	13 (3.6)	[redacted]
Herpes zoster	18 (5.0)	2 (0.6)	7 (1.9)	2 (0.6)
Pharyngitis	16 (4.4)	0	18 (5.0)	0
Oral candidiasis	14 (3.9)	[redacted]	18 (5.0)	[redacted]

In Study C16010, fatal infection was observed in 2 of 361 patients in the ixazomib/Ld group (0.6%, pneumonia and pneumonia fungal in 1 patient each) and in 4 of 359 patients in the placebo/Ld group (1.1%; cellulitis, sepsis, pneumonia pneumococcal, and pneumonia influenzal in 1 patient each). A causal relationship to the study drug could not be ruled out for pneumonia fungal (1 patient) in the ixazomib/Ld group. Serious infection was observed in 78 of 361 patients in the ixazomib/Ld group (21.6%; events reported by ≥5 patients were pneumonia [26 patients], bronchopneumonia, lower respiratory tract infection, and influenza [6 patients each]) and in 91 of 358 patients in the placebo/Ld group (25.3%; events reported by ≥5 patients were pneumonia [31 patients], bronchitis [8 patients], respiratory tract infection and septic shock [5 patients each]). A causal relationship to the study drug could not be ruled out for pneumonia (14 patients), bronchopneumonia (3 patients), influenza (2 patients), and lower respiratory tract infection (1 patient) in the ixazomib/Ld group; and pneumonia (22 patients), bronchitis (4 patients), septic shock (2 patients), and respiratory tract infection (1 patient) in the placebo/Ld group. Infection led to discontinuation of the study drug in 12 of 361 patients (3.3%) in the ixazomib/Ld group and in 10 of 359 patients (2.8%) in the placebo/Ld group, to interruption of the study drug in 70 of 361 patients (19.4%) in the ixazomib/Ld group and in 59 of 359 patients (16.4%) in the placebo/Ld group, and to dose reduction of the study drug in 11 of 361 patients (3.0%) in the ixazomib/Ld group and in 15 of 359 patients (4.2%) in the placebo/Ld group.

PMDA asked the applicant to explain the incidences of opportunistic infection (e.g., herpes virus infection, tuberculosis, reactivation of hepatitis B, and cytomegalovirus infection).

The applicant's explanation:
In Study C16010, herpes virus infection[30)] occurred in 36 of 361 patients (10.0%) in the ixazomib/Ld group and in 20 of 359 patients (5.6%) in the placebo/Ld group. The events were serious in 3 of 361 patients (0.8%) in the ixazomib/Ld group and in 2 of 359 patients (0.6%) in the placebo/Ld group. Tuberculosis[31)] occurred in [redacted] patients (0.3%) in the [redacted] group, which was considered to be serious in all of them and led to discontinuation of the study drug. Reactivation of hepatitis B occurred in [redacted] patients (0.3%) in the [redacted] group. Cytomegalovirus infection[32)] occurred in [redacted] patients (0.3%) in the [redacted] group, and considered serious in all of them. In Study C16010, no prophylactic administration had been prescribed against infection.

In clinical studies other than Study C16010,[29)] serious hepatitis B infection occurred in 1 patient. A causal relationship of the infection to ixazomib was ruled out.

PMDA's view:
In Study C16010, the incidence of infection did not tend to be clearly higher in the ixazomib/Ld group than in the placebo/Ld group. It is therefore difficult to draw any definite conclusion on the occurrences of infection due to ixazomib. However, the following information should be provided to healthcare

30) MedDRA PTs falling under "Herpes viral infections" in MedDRA HLT (MedDRA ver. 16.0) were tabulated.
31) MedDRA PTs falling under "Tuberculous infections" in MedDRA HLT (MedDRA ver. 16.0) were tabulated.
32) MedDRA PTs falling under "Cytomegaloviral infections" in MedDRA HLT (MedDRA ver. 16.0) were tabulated.

professionals, using the package insert, etc.: (a) The incidence of infection in the ixazomib/Ld group was high, and (b) the incidence of herpes virus infection was higher in the ixazomib/Ld group than in the placebo/Ld group. Also, the occurrences of infection associated with ixazomib should be further investigated, and new findings should be appropriately provided to healthcare professionals.

7.R.3.8 Encephalopathy

The applicant's explanation about encephalopathy associated with ixazomib:
As adverse events related to encephalopathy, MedDRA PTs corresponding to "Noninfectious encephalopathy/delirium (narrow)" in MedDRA SMQ (MedDRA ver. 16.0) were tabulated.

In Study C16010, all Grade encephalopathy was observed in [redacted] patients in the [redacted] group ([redacted]%, delirium and vascular encephalopathy in [redacted] patients each) and in [redacted] patients in the [redacted] group ([redacted]%; delirium in 3 patients, encephalopathy in [redacted] patients). Grade ≥3 encephalopathy was observed in [redacted] patients in the [redacted] group ([redacted]%, delirium and vascular encephalopathy in [redacted] patients each). Serious encephalopathy was observed in [redacted] patients in the [redacted] group ([redacted]%, delirium and vascular encephalopathy in [redacted] patients each). A causal relationship of delirium (1 patient) to the study drug could not be ruled out. Encephalopathy led to interruption of the study drug in [redacted] patients in the [redacted] group ([redacted]%, delirium in [redacted] patients) and in [redacted] patients in the [redacted] group ([redacted]%, encephalopathy in [redacted] patients). There was no encephalopathy that was fatal or led to discontinuation or dose reduction of the study drug.

In clinical studies other than Study C16010,[29)] there was no fatal encephalopathy. Serious encephalopathy was observed in 1 patient (posterior reversible encephalopathy syndrome), for which a causal relationship to ixazomib could not be ruled out.

PMDA's view:
Because of the limited occurrences of encephalopathy in Study C16010, there are limitations to the comparison of the incidences of encephalopathy between the ixazomib/Ld group and the placebo/Ld group, precluding conclusion on ixazomib-induced encephalopathy. However, posterior reversible encephalopathy syndrome with a suspected causal relationship to ixazomib was observed in a clinical study other than Study C16010, and this should be communicated to healthcare professionals using the package insert, etc. At the same time, ixazomib-induced encephalopathy should be further investigated and available new findings should be appropriately provided to healthcare professionals.

7.R.4 Clinical positioning

Descriptions of ixazomib for the treatment of relapsed or refractory MM in the Japanese and foreign clinical practice guidelines and in the representative textbooks of hematology and clinical oncology are described below. There was no description of ixazomib in the Clinical Practice Guidelines for Hematological Malignancy 2013 Edition (Kanehara & Co., Ltd., 2013), *New Medical Oncology*. Fourth revised edition, the Japanese Society of Medical Oncology, ed. (Nankodo Co., Ltd., 2015), or *Wintrobe's Clinical Hematology*. Thirteenth Edition (USA, Lippincott Williams & Wilkins, 2013).

Clinical Practice Guidelines

- National Comprehensive Cancer Network (NCCN) Guideline (v1.2017): Ixazomib/Ld therapy is recommended for patients with relapsed or refractory MM (Category 1[33)]).

- National Cancer Institute Physician Data Query Multiple Myeloma and Other Plasma Cell Neoplasms (NCI-PDQ), USA (November 4, 2016): In a randomized, comparative study in patients with relapsed or refractory MM, ixazomib/Ld therapy prolonged PFS compared with placebo/Ld therapy.

- Clinical Practice Guideline for Multiple Myeloma, Fourth edition, Japanese Society of Myeloma, ed. (Bunkodo Co., Ltd., 2016): In a randomized, comparative study in patients with relapsed or refractory MM, ixazomib/Ld therapy prolonged PFS compared with placebo/Ld therapy. Ixazomib/Ld therapy seldom causes peripheral nerve disorder, an event frequently observed in patients treated with

33) Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

bortezomib, and all drugs used in the therapy are oral medications, demonstrating the usefulness in maintaining quality of life (QOL) of patients and for convenience sake.

Textbook

- Williams Hematology, 9th Edition (USA, The McGraw-Hill Companies, Inc., 2015): A Phase III study is ongoing in patients with relapsed or refractory MM. All drugs included in ixazomib/Ld therapy are oral medications, which allow outpatient treatment thereby improving the QOL of patients.

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA discussed the clinical positioning of ixazomib as follows:
The results of PFS, etc. in Study C16010 did not demonstrate consistency in the efficacy of ixazomib between the Japanese population and the entire population [see Section "7.R.2 Efficacy"]. However, clinically significant PFS prolongation was observed in the entire population of Study C16010. In addition, by comprehensively taking account of the facts that (a) the therapeutic system of MM is similar among countries or regions that participated in Study C16010, that (b) no clear difference was observed in the PK of ixazomib between Japanese patients and non-Japanese patients [see Section "6.2.9 Difference in PK between Japanese and non-Japanese patients"], and that (c) ixazomib/Ld therapy was well tolerated in Japanese patients, ixazomib/Ld therapy is recognized as one of the treatment options for Japanese patients.

However, because of the limited available data on the efficacy of ixazomib in Japanese patients, relevant data should be further collected after the market launch, including data from the ongoing clinical studies below. Such information is critical in understanding the benefit-risk balance in selecting the treatment method in routine clinical practice in Japan. The data on the efficacy in Japanese patients obtained from Study C16010 should be appropriately provided to healthcare professionals using the package insert, etc.

- Global Phase III study to compare the efficacy and safety of ixazomib/Ld therapy and placebo/Ld therapy in patients with newly diagnosed MM (Study C16014)
- Japanese Phase II study to investigate the efficacy and safety of ixazomib/Ld therapy in Japanese patients with relapsed or refractory MM (Study C16028)

7.R.5 Indication

The proposed indication for ixazomib was "Relapsed or refractory multiple myeloma." The "Precautions for Indication" section contained the following requirements:

- Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.
- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert and of the efficacy and safety of ixazomib.

Following the review of Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning" and of the review described below, PMDA concluded that ixazomib should be indicated for "relapsed or refractory multiple myeloma," as proposed by the applicant. PMDA also concluded that the following descriptions should be included in the Precautions for Indication section:

- Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.
- Eligible patients should be selected based on a good understanding of the study result in the "Clinical Studies" section of the package insert, including prior regimens of patients enrolled in the clinical studies and of the efficacy and safety of ixazomib.

7.R.5.1 Target patients for treatment with ixazomib

The applicant's explanation about the target patients to be treated with ixazomib:

In Study C16010, the target patients were those with relapsed or refractory MM with 1 to 3 prior regimens for MM who met at least one of the following conditions. In Study C16010, patients who became unresponsive to lenalidomide or a proteasome inhibitor were excluded.

- The patient had a relapse after a prior regimen but was not unresponsive.
- The patient was unresponsive to all prior regimens (no response was obtained by any of the prior regimens).
- The patient had a relapse after receiving at least one regimen and became unresponsive to at least one of the regimens.

Table 31 shows the results of PFS, classified by the number of prior regimens, in Study C16010.

Table 31. Interim analysis of PFS (ITT population, IRC assessment, data cut-off October 30, 2014)

Number of regimens	Ixazomib/Ld		Placebo/Ld		Hazard ratio [95% CI]
	Number of patients	Median PFS [95% CI] (months)	Number of patients	Median PFS [95% CI] (months)	
Total	360	20.6 [17.0, NE]	362	14.7 [12.9, 17.6]	0.74 [0.59, 0.94]
1	224	20.6 [16.8, NE]	217	15.9 [13.2, 20.1]	0.83 [0.62, 1.12]
2	97	17.5 [15.7, NE]	111	14.1 [10.3, NE]	0.75 [0.48, 1.16]
3	39	NE [NE, NE]	34	10.2 [7.0, 13.9]	0.37 [0.17, 0.79]

In Study C16010, PFS of patients classified by the number of prior regimens was similar to that observed in the entire population. This suggests that ixazomib is recommended in patients with 1 to 3 prior regimens, the target patient population of Study C16010. In contrast, there are currently no clinical studies that have demonstrated the clinical benefits of ixazomib in patients with relapsed or refractory MM who were excluded from Study C16010, suggesting that ixazomib is not recommendable for such patients.

Based on the above, the target patients of ixazomib are those eligible for in Study C16010, and therefore proposed “relapsed or refractory multiple myeloma” as the indication for ixazomib, with the following cautions in the “Precautions for Indication” section:

- Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.
- Eligible patients should be selected based on a good understanding of the study results in the “Clinical Studies” section in the package insert and of the efficacy and safety of ixazomib.

PMDA’s view:
PMDA generally accepted the above explanation of the applicant, and concluded that the number of prior regimens administered to patients included in Study C16010 should be specified in the “Clinical Studies” section of the package insert, with the Precautions for Indication section modified as follows:

- Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regime.
- Eligible patients should be selected based on a good understanding of the study results in the “Clinical Studies” section of the package insert, including prior regimens of patients enrolled in the clinical studies, and of the efficacy and safety of ixazomib.

7.R.6 Dosage and administration

The proposed dosage and administration for ixazomib was “In combination with other antineoplastic drugs, the usual adult dosage is 4 mg of ixazomib administered orally under fasting conditions once weekly for 3 weeks (Day 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient’s condition.” Also, the following descriptions were included in the “Precautions for Dosage and Administration” section:

- Concomitant lenalidomide and DEX should be administered by physicians with a thorough understanding of contents in the “Clinical Studies” section and the package inserts of the concomitant drugs should be read carefully.

- The efficacy and safety of ixazomib used in combination with antineoplastic drugs other than lenalidomide and DEX have not been established.

- The AUC of ixazomib increases in patients with moderate or severe hepatic impairment and in patients with severe renal impairment or with end-stage renal failure requiring hemodialysis. It is recommended to reduce the dose to 3 mg in these patients.

- The administration of ixazomib after intake of a high-fat diet decreases C_{max} and AUC of ixazomib. Ixazomib should be administered ≥1 hour before or ≥2 hours after meals.

- Criteria for interruption, dose reduction, or discontinuation of ixazomib in case of an adverse drug reaction, and criteria for starting a new treatment cycle

As a result of the review of Sections "6.R.1 Food effect," "6.R.2 Ixazomib administration in patients with renal impairment," "6.R.3 Ixazomib administration in patients with hepatic impairment," "7.R.2 Efficacy," and "7.R.3 Safety" and of the review described below, PMDA concluded that the following statements should be included in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections of package insert.

Dosage and Administration
In combination with lenalidomide and dexamethasone, the usual adult dosage is 4 mg of ixazomib administered orally once daily under fasting conditions once weekly for 3 weeks (Days 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient's condition.

Precautions for Dosage and Administration
- The efficacy and safety of ixazomib monotherapy have not been established.

- Concomitant lenalidomide and DEX should be administered by physicians with a thorough understanding of contents in the "Clinical Studies" section and the package inserts of the concomitant drugs should be read carefully.

- The efficacy and safety of ixazomib used in combination with antineoplastic drugs other than lenalidomide and DEX have not been established.

- Patients with moderate or severe hepatic impairment and in patients with severe renal impairment are known to have increased blood ixazomib concentration. Dose reduction may be considered in treating these patients, and they must be closely monitored for possible adverse events.

- C_{max} and AUC of ixazomib are known to be decreased when administered after meal. Ixazomib should not be administered 1 hour before until 2 hours after meals to avoid food effect.

- Before starting a new treatment cycle, the use of ixazomib should be determined based on the following criteria.

Criteria for starting a new treatment cycle

Neutrophil count	≥1000/mm^3
Platelet count	≥75,000/mm^3
Non-hematologic toxicity	Baseline or Grade ≤1

Grading is based on NCI-CTCAE v4.0.

- In case of an ixazomib-induced adverse drug reaction, treatment should be withheld or discontinued, or the dose of ixazomib should be reduced according to the following criteria.

Steps for ixazomib dose reduction

Starting dose	4 mg
Step 1 (1-level lower dose)	3 mg
Step 2 (2-level lower dose)	2.3 mg
Step 3	Discontinue

Criteria for dose suspension, reduction, and discontinuation

Adverse drug reaction	Severity	Measures taken
Thrombocytopenia	Platelet count <30,000/mm^3	Withhold ixazomib until platelet count recovers to ≥30,000/mm^3. After recovery, resume ixazomib at its most recent dose. If platelet count decreases to <30,000/mm^3 again, withhold ixazomib until it recovers to ≥30,000/mm^3. After recovery, resume ixazomib at the next lower dose.
Neutropenia	Neutrophil count <500/mm^3	Withhold ixazomib until neutrophil count recovers to ≥500/mm^3. After recovery, resume ixazomib at its most recent dose. If neutrophil count has decreases to <500/mm^3 again, withhold ixazomib until it recovers to ≥500/mm^3. After recovery, resume ixazomib at the next lower dose.
Skin disorder	Grade 2	Give a symptomatic treatment for skin disorder and continue ixazomib. If the symptom is intolerable, follow "Grade 3".
	Grade 3	Withhold ixazomib until the symptom recovers to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue treatment.
Peripheral nerve disorder	Grade 1 with pain, or Grade 2 without pain	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1 without pain. After recovery, resume ixazomib at its most recent dose.
	Grade 2 with pain, or Grade 3	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue ixazomib.
Other adverse drug reactions	Grade 3 non-hematological toxicity	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4 non-hematological toxicity	Discontinue ixazomib.

Grading is based on NCI-CTCAE v4.0.

7.R.6.1 Dosage and administration of ixazomib

The applicant's explanation about the dosage and administration of ixazomib:

In Study C16005 in patients with newly diagnosed MM, the safety, etc. of ixazomib was investigated by administering oral ixazomib on Days 1, 8, and 15 in each 28-day treatment cycle in tune with the treatment cycle of co-administered Ld regimen.[14)] Results showed that ixazomib at a dose of 2.23 or 2.97 mg/m^2 is expected to be clinically effective when used with Ld regimen, and that there is no clear difference in the efficacy or safety of ixazomib between the two doses. However, since a possibility was suggested that the dose of lenalidomide may have to be reduced at 2.97 mg/m^2 of ixazomib, the dose of ixazomib of 2.23 mg/m^2 was recommended in concomitant use with Ld regimen. Also, results of PPK analysis based on PK data of ixazomib (3579 measuring time points in 226 patients) obtained from foreign Phase I studies (Studies C16001, C16002, C16003, and C16004) suggested there is no correlation between CL of ixazomib and body surface area.

Based on the above results and on the fixed dose of 4.0 mg calculated from the dose 2.23 mg/m^2 by assuming the body surface area to be 1.86 m^2, the dosage and administration in Study C16010 was "oral ixazomib 4.0 mg QD in combination with Ld regimen on Days 1, 8, and 15 in each 28-day treatment cycle."

Results of Study C16010 conducted under the above regimens demonstrated the clinical benefit of ixazomib in relapsed or refractory MM. Therefore, the proposed dosage and administration of ixazomib was the same as that used in this study.

PMDA's view:

PMDA generally accepted the applicant's explanation. However, the clinical benefits of ixazomib have been demonstrated only in its concomitant use with Ld regimen in patients with relapsed or refractory MM. The "Dosage and Administration" section should therefore highlight that ixazomib should be

administered in combination with lenalidomide and DEX.

7.R.6.2 Dose adjustment of ixazomib

The applicant's explanation about the dose adjustment of ixazomib:
Study C16010 demonstrated the good tolerability of ixazomib when administered according to criteria for starting a new treatment cycle and for interruption, dose reduction, and discontinuation of ixazomib established. Therefore, the Precautions for Dosage and Administration section included criteria for starting a new treatment cycle and for interruption, dose reduction, and discontinuation of ixazomib as per Study C16010. Thrombocytopenia is considered an adverse event common to ixazomib and lenalidomide. Therefore, following the treatment suspension due to thrombocytopenia, ixazomib and lenalidomide were resumed at doses that were reduced alternately according to the frequency the adverse event. The "Precautions for Dosage and Administration" section, however, mentions dose adjustment criteria of ixazomib only. The differences in the dose adjustment criteria in the package insert from those used in Study C16010 and reasons for the changes are as follows.

- Even though criteria for ixazomib dose adjustment were defined for neutropenia in Study C16010, the incidence of neutropenia in the study was similar[34)] between the ixazomib/Ld group and placebo/Ld group. The criteria were therefore not indicated in the package insert.
- The criteria in Study C16010 required ixazomib to be suspended following Grade 2 rash. However, a certain proportion of patients in the ixazomib/Ld group experiencing Grade ≥2 rash were controlled only by symptomatic treatment requiring no suspension or dose reduction of either drug. Therefore, the package insert noted that treatment suspension is not necessary for Grade 2 rash controllable by symptomatic treatment.
- The criteria in Study C16010 required ixazomib to be discontinued following Grade 4 non-hematologic toxicity other than rash and peripheral nerve disorder. However, some patients in the ixazomib/Ld group suffering with Grade 4 non-hematological toxicity during the study continued the treatment without having to discontinue either drug Therefore, the package insert instructs that patients experiencing Grade 4 non-hematological toxicity other than rash and peripheral nerve disorder should follow the dose adjustment criteria for the mentioned adverse events of Grade 3.

PMDA's view:
The applicant's above explanation about the criteria for dose adjustment for Grade 2 rash is acceptable. However, in light of the following observations, the dose adjustment criteria for neutropenia and for Grade 4 non-hematological toxicity should be defined based on the criteria in Study C16010.

- In Study C16010, neutropenia and febrile neutropenia with a suspected causal relationship to ixazomib occurred.
- Grade 4 non-hematological toxicity other than rash and peripheral nerve disorder occurred in Study C16010 included serious adverse events such as sepsis and myocardial infarction.
- In the Japanese Phase I study (Study TB-MC010034), the incidence of neutropenia was high both in the ixazomib monotherapy group and in the ixazomib/Ld therapy group.

PMDA concluded that dose adjustment criteria of ixazomib should be defined based on these observations in the "Precautions for Dosage and Administration" section, and that information on the dose adjustment criteria including those of concomitant drugs used in Study C16010 should be appropriately communicated to healthcare professionals using written materials.

7.R.6.3 Ixazomib monotherapy and combination therapy with antineoplastic drugs other than the Ld regimen

The applicant's explanation about ixazomib monotherapy and combination therapy with antineoplastic drugs other than Ld regimen[14)]:
Since there are no clinical study data of patients with relapsed or refractory MM on the efficacy and safety of ixazomib monotherapy or of combination therapy with antineoplastic drugs other than Ld

34) The incidence of all-grade neutropenia was 26% and 22%, and Grade ≥3 neutropenia was 15% and 12% in the ixazomib/Ld group and in the placebo/Ld group, respectively.

regimen, neither of these regimens is recommended. Therefore, the "Dosage and Administration" section will advise that ixazomib should be administered in combination with other antineoplastic drugs. The "Precautions for Dosage and Administration" section should highlight that efficacy and safety in concomitant use with antineoplastic drugs other than lenalidomide and DEX have not been established.

PMDA's view:
The applicant's explanation is generally acceptable. However, the "Dosage and Administration" section should clearly remind of the need for concomitant lenalidomide and DEX [see Section "7.R.6.1 Dosage and administration of ixazomib]. The "Precautions for Dosage and Administration" section should also remind clearly of no established efficacy and safety of ixazomib monotherapy.

7.R.7 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:
In order to evaluate the safety, etc. of ixazomib in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with ixazomib.

Key survey items of the post-marketing surveillance include Grade ≥3 rash[35)], in addition to events defined as important identified risks in safety specification in the proposed risk management plan (draft) (thrombocytopenia, severe gastrointestinal disorder [nausea, vomiting, diarrhoea], and peripheral nerve disorder) for the following reasons:

- In Study C16010, the incidence of Grade ≥3 rash was higher in the Japanese population (25%) than in the entire population (5%).
- In case of Grade ≥3 rash, clinical control such as dose adjustment is important.

The planned sample size was 480 subjects. The surveillance will focus on the occurrences of Grade ≥3 rash, which is one of the key survey items, in an early stage of the treatment. Considering that of Grade ≥3 rash is likely to occur within 3 months after the start of ixazomib in Study C16010, the sample size of 480 will give sufficient statistic power to detect Grade ≥3 rash as well as other events specified as the key survey items.

The follow-up period is 6 treatment cycles after the start of treatment with ixazomib, based on the fact that the events specified as the key survey items occurred mostly within 6 treatment cycles (24 weeks) after the start of ixazomib and that the incidences of these events did not tend to increase with continued treatment with ixazomib.

PMDA's view:
Because of extremely limited data on the safety of ixazomib/Ld therapy in Japanese patients with relapsed or refractory MM, surveillance covering all patients treated with ixazomib is essential for a certain post-marketing period. Safety data should be collected promptly in an unbiased manner, and newly available safety data should be communicated to healthcare professionals without delay.
Appropriate key survey items of the surveillance are thrombocytopenia, severe gastrointestinal disorder, peripheral nerve disorder, skin disorder, and infection, according to the incidences of adverse events in Japanese and foreign clinical studies. The planned sample size and the follow-up period should be re-examined in light of the incidences of additional key survey items in clinical studies.

Post-marketing efficacy data of ixazomib should be continuously collected from Japanese patients receiving the treatment, based on the review in Section "7.R.4 Clinical positioning."

7.3 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections "7.1 Evaluation data" and in "7.2 Reference data." The following subsections summarize major non-fatal adverse events.

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35) The following PTs in MedDRA (MedDRA ver. 16.0) were regarded as rash: Acute febrile neutrophilic dermatosis, dermatitis acneform, dermatitis allergic, drug eruption, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, pruritus, pruritus generalized, purpura, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash popular, rash pruritic, rash pustular, rash vesicular, red man syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, urticaria popular, and vasculitic rash.

7.3.1 Japanese Phase I study (Study TB-MC010034)

Adverse events were observed in all patients. Adverse events with a suspected causal relationship to the study drug were observed in 7 of 7 patients (100%) in the ixazomib monotherapy cohort and in 6 of 7 patients (85.7%) in the combination therapy cohort. Table 32 shows adverse events with an incidence of ≥40% in either group.

Table 32. Adverse events with an incidence of ≥40% in either group

SOC PT (MedDRA/J ver. 16.0)	Number of patients			
	Monotherapy		Combination therapy	
	N = 7		N = 7	
	All grades	Grades ≥3	All grades	Grades ≥3
All adverse events	7 (100)	7 (100)	7 (100)	5 (71.4)
Infections and infestations				
Bronchitis	2 (28.6)	0	3 (42.9)	1 (14.3)
Blood and lymphatic system disorders				
Neutropenia	6 (85.7)	4 (57.1)	5 (71.4)	4 (57.1)
Thrombocytopenia	6 (85.7)	3 (42.9)	4 (57.1)	4 (57.1)
Leukopenia	5 (71.4)	2 (28.6)	4 (57.1)	1 (14.3)
Lymphopenia	6 (85.7)	5 (71.4)	2 (28.6)	2 (28.6)
Metabolism and nutrition disorders				
Decreased appetite	3 (42.9)	0	0	0
Psychiatric disorders				
Insomnia	3 (42.9)	0	2 (28.6)	0
Gastrointestinal disorders				
Diarrhoea	6 (85.7)	2 (28.6)	4 (57.1)	1 (14.3)
Vomiting	5 (71.4)	1 (14.3)	3 (42.9)	0
Nausea	5 (71.4)	1 (14.3)	2 (28.6)	0
Skin and subcutaneous tissue disorders				
Rash maculo-papular	3 (42.9)	0	0	0
General disorders and administration site conditions				
Pyrexia	3 (42.9)	0	1 (14.3)	0

Serious adverse events occurred in 3 of 7 patients (42.9%) in the monotherapy cohort and in 1 of 7 patients (14.3%) in the combination therapy cohort. Serious adverse events were bronchitis, retinal detachment, hypokalaemia, and thrombocytopenia in 1 patient (14.3%) each in the monotherapy cohort and bone pain in 1 patient (14.3%) in the combination therapy cohort. A causal relationship to the study drug could not be ruled out for bronchitis, hypokalaemia, and thrombocytopenia (1 patient each) in the monotherapy cohort.

Adverse events led to discontinuation of the study drug in 1 of 7 patients (14.3%) in the monotherapy cohort and 2 of 7 patients (28.6%) in the combination therapy cohort. Diarrhoea occurred in 1 patient (14.3%) in the monotherapy cohort, and neutropenia and thrombocytopenia in 2 patients (28.6%) each in the combination therapy cohort. A causal relationship to the study drug could not be ruled out for diarrhoea (1 patient) in the monotherapy cohort and thrombocytopenia (2 patients) and neutropenia (1 patient) in the combination therapy cohort.

7.3.2 Global Phase III study (Study C16010)

Adverse events were observed in 355 of 361 patients (98.3%) in the ixazomib/Ld group and in 357 of 359 patients (99.4%) in the placebo/Ld group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 335 of 361 patients (92.8%) in the ixazomib/Ld group and 329 of 359 patients (91.6%) in the placebo/Ld group. Table 33 shows adverse events with an incidence of ≥20% in either group.

Table 33. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA/J ver. 16.0)	Number of patients			
	Ixazomib/Ld		Placebo/Ld	
	N = 361		N= 359	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	355 (98.3)	267 (74.0)	357 (99.4)	247 (68.8)
Infections and infestations				
Upper respiratory tract infection	83 (23.0)	2 (0.6)	70 (19.5)	3 (0.8)
Nasopharyngitis	81 (22.4)	0	73 (20.3)	0
Blood and lymphatic system disorders				
Neutropenia	103 (28.5)	74 (20.5)	92 (25.6)	71 (19.8)
Thrombocytopenia	86 (23.8)	55 (15.2)	41 (11.4)	22 (6.1)
Anaemia	103 (28.5)	34 (9.4)	98 (27.3)	48 (13.4)
Psychiatric disorders				
Insomnia	73 (20.2)	7 (1.9)	98 (27.3)	11 (3.1)
Gastrointestinal disorders				
Diarrhoea	164 (45.4)	23 (6.4)	139 (38.7)	9 (2.5)
Nausea	104 (28.8)	[redacted]	79 (22.0)	[redacted]
Vomiting	84 (23.3)	4 (1.1)	42 (11.7)	2 (0.6)
Constipation	126 (34.9)	1 (0.3)	94 (26.2)	1 (0.3)
Musculoskeletal and connective tissue disorders				
Back pain	87 (24.1)	3 (0.8)	62 (17.3)	9 (2.5)
Muscle spasms	66 (18.3)	[redacted]	95 (26.5)	[redacted]
General disorders and administration site conditions				
Fatigue	106 (29.4)	13 (3.6)	102 (28.4)	10 (2.8)
Oedema peripheral	101 (28.0)	8 (2.2)	73 (20.3)	4 (1.1)
Pyrexia	56 (15.5)	4 (1.1)	75 (20.9)	7 (1.9)

Serious adverse events occurred in 168 of 361 patients (46.5%) in the ixazomib/Ld group and 177 of 359 patients (49.3%) in the placebo/Ld group. Serious adverse events reported by ≥8 patients in either group were pneumonia (26 patients [7.2%]), pyrexia (12 patients [3.3%]), and plasma cell myeloma and diarrhoea (9 patients each [2.5%]) in the ixazomib/Ld group; and pneumonia (31 patients [8.6%]), pyrexia (16 patients [4.5%]), pulmonary embolism (9 patients [2.5%]), and plasma cell myeloma, anaemia, bronchitis, and febrile neutropenia (8 patients each [2.2%]) in the placebo/Ld group. A causal relationship to the study drug could not be ruled out for pneumonia (14 patients), diarrhoea (7 patients), and pyrexia (6 patients) in the ixazomib/Ld group; and for pneumonia (22 patients), pulmonary embolism (9 patients), pyrexia, anaemia, and febrile neutropenia (5 patients each), and bronchitis (4 patients) in the placebo/Ld group.

Adverse events led to discontinuation of the study drug in 91 of 361 patients (25.2%) in the ixazomib/Ld group and 73 of 359 (20.3%) in the placebo/Ld group. Adverse events leading to treatment discontinuation reported by ≥4 patients in either group were peripheral sensory neuropathy (7 patients [1.9%]), diarrhoea (6 patients [1.7%]), fatigue (5 patients [1.4%]), and plasma cell myeloma and thrombocytopenia (4 patients each [1.1%]) in the ixazomib/Ld group; and insomnia (6 patients [1.7%]), and thrombocytopenia and cardiac failure (4 patients each [1.1%]) in the placebo/Ld group. A causal relationship to the study drug could not be ruled out for peripheral sensory neuropathy (7 patients), diarrhoea (5 patients), fatigue (4 patients), and thrombocytopenia (3 patients) in the ixazomib/Ld group; and insomnia (6 patients), cardiac failure (3 patients), and thrombocytopenia (2 patients) in the placebo/Ld group.

7.3.3 Foreign Phase I study (Study C16009)

Adverse events occurred in 29 of 29 patients (100%) in Group 1, 20 of 20 patients (100%) in Group 2, 24 of 24 patients (100%) in Group 3, 17 of 18 patients (94.4%) in Group 4, and 16 of 21 patients (76.2%) in Group 5. Adverse events with a suspected causal relationship to ixazomib occurred in 27 of 29 patients (93.1%) in Group 1, 17 of 20 patients (85.0%) in Group 2, 20 of 24 patients (83.3%) in Group 3, 15 of 18 patients (83.3%) in Group 4, and 4 of 21 patients (19.0%) in Group 5. Adverse events with an incidence of ≥30% in any group were nausea (21 patients [72.4%]), fatigue (20 patients [69.0%]), diarrhoea (19 patients [65.5%]), vomiting (18 patients [62.1%]), decreased appetite (13 patients [44.8%]), constipation (12 patients [41.4%]), asthenia (11 patients [37.9%]), and dehydration (10

patients [34.5%]) in Group 1; nausea (11 patients [55.0%]), vomiting (8 patients [40.0%]), decreased appetite, diarrhoea, and fatigue (7 patients each [35.0%]), and constipation (6 patients [30.0%]) in Group 2; vomiting (15 patients [62.5%]), nausea (12 patients [50.0%]), fatigue (9 patients [37.5%]), and oedema peripheral (8 patients [33.3%]) in Group 3; and nausea (8 patients [44.4%]) and fatigue (7 patients [38.9%]) in Group 4.

Serious adverse events occurred in 12 of 29 patients (41.4%) in Group 1, 5 of 20 patients (25.0%) in Group 2, 12 of 24 patients (50.0%) in Group 3, 2 of 18 patients (11.1%) in Group 4, and 2 of 21 patients (9.5%) in Group 5. Serious adverse events reported by ≥2 patients in any group were dehydration (3 patients [10.3%]) in Group 1, small intestinal obstruction (2 patients [10.0%]) in Group 2, and dehydration and endometrial cancer (2 patients each [8.3%]) in Group 3. A causal relationship to ixazomib could not be ruled out for dehydration (2 patients) in Group 1 and dehydration (1 patient) in Group 3.

Adverse events led to discontinuation of ixazomib in 8 of 29 patients (27.6%) in Group 1, 3 of 20 patients (15.0%) in Group 2, 7 of 24 patients (29.2%) in Group 3, 1 of 18 patients (5.6%) in Group 4, and 1 of 21 patients (4.8%) in Group 5. The adverse events leading to discontinuation of the study drug reported by ≥2 patients in any group were fatigue (2 patients [6.9%]) in Group 1 and endometrial cancer (2 patients [8.3%]) in Group 3. A causal relationship to ixazomib could not be ruled out for fatigue (1 patient) in Group 1.

7.3.4 Foreign Phase I study (Study C16016)

Adverse events occurred in all patients. Adverse events with a suspected causal relationship to the study drug were observed in 6 of 7 patients (85.7%). Adverse events with an incidence of ≥20% were diarrhoea (4 patients [57.1%]), headache (3 patients [42.9%]), decreased appetite, dizziness, abdominal pain upper, vomiting, constipation, pruritus, rash maculo-papular, and back pain (2 patients each [28.6%]).

A serious adverse event occurred in 1 of 7 patients (14.3%). The observed serious adverse event was influenza (1 patient [14.3%]), and its causal relationship to the study drug was ruled out.

There was no adverse event leading to discontinuation of the study drug.

7.3.5 Foreign Phase I study (Study C16013)

Adverse events occurred in all patients. Adverse events with a suspected causal relationship to the study drug occurred in 37 of 43 patients (86.0%). Adverse events with an incidence of ≥20% were diarrhoea (23 patients [53.5%]), upper respiratory tract infection (14 patients [32.6%]), vomiting (13 patients [30.2%]), neutropenia, thrombocytopenia, decreased appetite, cough, and fatigue (12 patients each [27.9%]), dizziness (11 patients [25.6%]), anaemia and nausea (10 patients each [23.3%]), and insomnia, neuropathy peripheral, and pyrexia (9 patients each [20.9%]).

Serious adverse events occurred in 18 of 43 patients (41.9%). Serious adverse events reported by ≥2 patients were pneumonia and diarrhoea (3 patients each [7.0%]), lung infection, back pain, plasmacytoma, and upper respiratory tract infection (2 patients each [4.7%]). A causal relationship to the study drug could not be ruled out for diarrhoea (3 patients), pneumonia (2 patients), and back pain (1 patient).

Adverse events led to discontinuation of the study drug in 7 of 43 patients (16.3%). They were pneumonia (2 patients [4.7%]), drug hypersensitivity, neuropathy peripheral, plasmacytoma, renal impairment, spinal cord compression, and thrombocytopenia (1 patient each [2.3%]). A causal relationship to the study drug could not be ruled out for pneumonia, drug hypersensitivity, neuropathy peripheral, renal impairment, and thrombocytopenia (1 patient each).

7.3.6 Foreign Phase I study (Study C16015)

Adverse events occurred in 19 of 20 patients (95.0%) with normal renal function, 14 of 14 patients (100%) with severe renal impairment, and 6 of 7 patients (85.7%) with end-stage renal failure. Adverse events with a suspected causal relationship to ixazomib occurred in 16 of 20 patients (80.0%) with

normal renal function, 12 of 14 patients (85.7%) with severe renal impairment, and 4 of 7 patients (57.1%) with end-stage renal failure. Adverse events with an incidence of ≥20% in any group were diarrhoea (8 patients [40.0%]), nausea (7 patients [35.0%]), fatigue and vomiting (5 patients each [25.0%]), and constipation, upper respiratory tract infection, and headache (4 patients each [20.0%]) among patients with normal renal function; diarrhoea and fatigue (6 patients each [42.9%]), nausea, vomiting, and anaemia (5 patients each [35.7%]), oedema peripheral (4 patients [28.6%]), and dyspnoea, dizziness, hypotension, and platelet count decreased (3 patients each [21.4%]) among patients with severe renal impairment; and vomiting, anaemia, and hypokalaemia (2 patients each [28.6%]) among patients with end-stage renal failure.

Serious adverse events occurred in 2 of 20 patients (10.0%) with normal renal function, 6 of 14 patients (42.9%) with severe renal impairment, and 4 of 7 patients (57.1%) with end-stage renal failure. They were hypoglycaemia, renal failure acute, pyrexia, bacteraemia, and bronchitis (1 patient each [5.0%]) among patients with normal renal function; gastrooesophageal cancer, dyspnoea, dehydration, pancreatitis acute, respiratory failure, sepsis, pneumonia, hyperkalaemia, skin infection, anaemia, confusional state, hypotension, and blood creatinine increased (1 patient each [7.1%]) among patients with severe renal impairment; and plasma cell myeloma, vomiting, dyspnoea, and gastrointestinal haemorrhage (1 patient each [14.3%]) among patients with end-stage renal failure. A causal relationship to ixazomib could not be ruled out for renal failure acute (1 patient with normal renal function); dehydration, pancreatitis acute, respiratory failure, sepsis, and blood creatinine increased (1 patient each with severe renal impairment); and vomiting (1 patient with end-stage renal failure).

Adverse events led to discontinuation of ixazomib in 2 of 20 patients (10.0%) with normal renal function and 4 of 14 patients (28.6%) with severe renal impairment. They were peripheral sensory neuropathy and malaise (1 patient each [5.0%] with normal renal function) and neuropathy peripheral, pancreatitis acute, pneumonia, and gastrooesophageal cancer (1 patient each [7.1%] with severe renal impairment). A causal relationship to ixazomib could not be ruled out for these events, except pneumonia and gastrooesophageal cancer (1 patient each with severe renal impairment).

7.3.7 Foreign Phase I study (Study C16018)

Adverse events occurred in all patients. Adverse events with a suspected causal relationship to ixazomib observed in 10 of 13 patients (76.9%) with normal hepatic function, 7 of 15 patients (46.7%) with moderate hepatic impairment, and 5 of 20 patients (25.0%) with severe hepatic impairment. Adverse events with an incidence of ≥20% in any group were nausea (9 patients [69.2%]), decreased appetite and vomiting (7 patients each [53.8%]), fatigue (6 patients [46.2%]), dyspnoea and diarrhoea (4 patients each [30.8%]), and urinary tract infection, dehydration, and insomnia (3 patients each [23.1%]) in patients with normal hepatic function; oedema peripheral (9 patients [60.0%]), hyperbilirubinaemia (5 patients [33.3%]), nausea and fatigue (4 patients each [26.7%]), and anaemia, dyspnoea, and ascites (3 patients each [20.0%]) in patients with moderate hepatic impairment; and renal failure acute (6 patients [30.0%]), nausea, hyperbilirubinaemia, and fatigue (5 patients each [25.0%]), and hypotension, dyspnoea, vomiting, oedema peripheral, and pyrexia (4 patients each [20.0%]) in patients with severe hepatic impairment.

Serious adverse events occurred in 6 of 13 patients (46.2%) with normal hepatic function, 10 of 15 patients (66.7%) with moderate hepatic impairment, and 15 of 20 patients (75.0%) with severe hepatic impairment. Serious adverse events reported by ≥2 patients in any group were pulmonary embolism and dehydration (2 patients each [13.3%]) in patients with moderate hepatic impairment; and renal failure acute (6 patients [30.0%]) and mental status changes (2 patients [10.0%]) in patients with severe hepatic impairment. A causal relationship to ixazomib could not be ruled out for dehydration (2 patients with moderate hepatic impairment).

Adverse events led to discontinuation of ixazomib administration in 2 of 13 patients (15.4%) with normal hepatic function, 1 of 15 patients (6.7%) with moderate hepatic impairment, and 3 of 20 patients (15.0%) with severe hepatic impairment. Confusional state, axillary pain, and groin pain occurred in patients with normal hepatic function (1 patient each [7.7%]); peritoneal haemorrhage in patients with moderate hepatic impairment (1 patient [6.7%]); and acute hepatic failure, pancreatic carcinoma, and

renal failure acute in patients with severe hepatic impairment (1 patient each [5.0%]). A causal relationship to ixazomib was ruled out for all events.

7.3.8 Foreign Phase I study (Study C16003)

Adverse events occurred in all patients. Adverse events with a suspected causal relationship to ixazomib were observed in 21 of 26 patients (80.8%) in the dose titration part and 38 of 40 patients (95.0%) in the expansion part. Adverse events with an incidence of ≥30% in either part were nausea and fatigue (12 patients each [46.2%]), upper respiratory tract infection (11 patients [42.3%]), thrombocytopenia, diarrhoea, and vomiting (10 patients each [38.5%]), and cough (8 patients [30.8%]) in the dose titration part; and fatigue (23 patients [57.5%]), nausea (21 patients [52.5%]), thrombocytopenia (20 patients [50.0%]), diarrhoea and pyrexia (15 patients each [37.5%]), and decreased appetite (13 patients [32.5%]) in the expansion part.

Serious adverse events occurred in 11 of 26 patients (42.3%) in the dose titration part and 24 of 40 patients (60.0%) in the expansion part. Serious adverse events reported by ≥2 patients in either part were thrombocytopenia (3 patients [11.5%]) and dehydration (2 patients [7.7%]) in the dose titration part; and thrombocytopenia, pneumonia, and pyrexia (5 patients each [12.5%]), dehydration (4 patients [10.0%]), hypoxia (3 patients [7.5%]), and abdominal pain, bone pain, hypotension, and renal failure acute (2 patients each [5.0%]) in the expansion part. A causal relationship to ixazomib could not be ruled out for thrombocytopenia (2 patients) in the dose titration part and for thrombocytopenia (5 patients), pyrexia (4 patients), dehydration and abdominal pain (2 patients each), and pneumonia, hypoxia, and hypotension (1 patient each) in the expansion part.

Adverse events led to discontinuation of ixazomib in 1 of 26 patients (3.8%) in the dose titration part and 8 of 40 patients (20.0%) in the expansion part. Spinal cord compression (1 patient [3.8%]) was observed in the dose titration part, and thrombocytopenia, bone pain, fall, fatigue, nausea, neuropathy peripheral, pneumonia, rash pruritic, pulmonary hypertension, and spinal cord compression (1 patient each [2.5%]) were observed in the expansion part. A causal relationship to ixazomib could not be ruled out for thrombocytopenia, fall, nausea, fatigue, pulmonary hypertension, and rash pruritic (1 patient each) in the expansion part.

7.3.9 Foreign Phase I study (Study C16004)

Adverse events occurred in 31 of 32 patients (96.9%) in the dose titration part and 31 of 31 patients (100%) in the expansion part. A causal relationship to ixazomib could not be ruled out for the events in 26 of 32 patients (81.3%) in the dose titration part and 28 of 31 patients (90.3%) in the expansion part. Adverse events with an incidence of ≥30% in either part were fatigue (17 patients [53.1%]), thrombocytopenia (14 patients [43.8%]), nausea (13 patients [40.6%]), diarrhoea (12 patients [37.5%]), and vomiting (11 patients [34.4%]) in the dose titration part; and thrombocytopenia, diarrhoea, and fatigue (17 patients each [54.8%]), nausea (15 patients [48.4%]), decreased appetite and vomiting (14 patients each [45.2%]), neutropenia (11 patients [35.5%]), and lymphopenia and anaemia (10 patients each [32.3%]) in the expansion part.

Serious adverse events occurred in 7 of 32 patients (21.9%) in the dose titration part and in 15 of 31 patients (48.4%) in the expansion part. Serious adverse events reported by ≥2 patients in either part were diarrhoea (3 patients [9.4%]), and nausea and vomiting (2 patients each [6.3%]) in the dose titration part; and diarrhoea and pneumonia (4 patients each [12.9%]), and hypercalcaemia, dehydration, and pyrexia (2 patients each [6.5%]) in the expansion part. A causal relationship to ixazomib could not be ruled out for these events except pneumonia, hypercalcaemia, and pyrexia (2 patients each) and diarrhoea (1 patient) in the expansion part.

Adverse events led to discontinuation of ixazomib in 4 of 32 patients (12.5%) in the dose titration part and in 4 of 31 (12.9%) in the expansion part. They were diarrhoea, thrombocytopenia, blood creatinine increased, nausea, and vomiting (1 patient each [3.1%]) in the dose titration part; and diarrhoea, hypercalcaemia, renal failure, and dyspnoea (1 patient each [3.2%]) in the expansion part. A causal relationship to ixazomib could not be ruled out for these events except blood creatinine increased (1 patient) in the dose titration part and hypercalcaemia (1 patient) in the expansion part.

7.3.10 Foreign Phase I/II study (Study C16005)

7.3.10.1 Phase I

Adverse events occurred in all patients. All patients experienced an adverse event with a suspected causal relationship to the study drug. Adverse events with an incidence of ≥40% in any group were hypotension, constipation, and muscle spasms (2 patients each [66.7%]) in the 1.68 mg/m^2 group; upper respiratory tract infection, abdominal discomfort, muscle spasms, fatigue, and oedema peripheral (2 patients each [66.7%]) in the 2.23 mg/m^2 group; diarrhoea (5 patients [83.3%]), vomiting (4 patients [66.7%]), upper respiratory tract infection, dizziness, nausea, rash maculo-papular, arthralgia, and pain in extremity (3 patients each [50.0%]) in the 2.97 mg/m^2 group; and diarrhoea, vomiting, and nausea (3 patients each [100%]), anaemia, thrombocytopenia, hypokalaemia, decreased appetite, dizziness, neuropathy peripheral, syncope, cough, rash maculo-papular, and oedema peripheral (2 patients each [66.7%]) in the 3.95 mg/m^2 group.

Serious adverse events occurred in 2 of 3 patients (66.7%) in the 1.68 mg/m^2 group, 3 of 3 patients (100%) in the 2.23 mg/m^2 group, 1 of 6 patients (16.7%) in the 2.97 mg/m^2 group, and 2 of 3 patients (66.7%) in the 3.95 mg/m^2 group. Gastrointestinal haemorrhage and hypotension occurred in 1 patient each (33.3%) in the 1.68 mg/m^2 group; deep vein thrombosis, pyrexia, hyponatraemia, and atrial fibrillation in 1 patient each (33.3%) in the 2.23 mg/m^2 group; pneumonia in 1 patient (16.7%) in the 2.97 mg/m^2 group; and rash maculo-papular, orthostatic hypotension, nausea, vomiting, asthenia, dizziness, diarrhoea, dehydration, neuropathy peripheral, hypovolaemia, and syncope in 1 patient each (33.3%) in the 3.95 mg/m^2 group. A causal relationship to the study drug could not be ruled out for deep vein thrombosis, hyponatraemia, and atrial fibrillation (1 patient each) in the 2.23 mg/m^2 group; rash maculo-papular, orthostatic hypotension, nausea, vomiting, asthenia, dizziness, diarrhoea, dehydration, neuropathy peripheral, hypovolaemia, and syncope (1 patient each) in the 3.95 mg/m^2 group.

Adverse events led to discontinuation of the study drug in 1 of 3 patients (33.3%) in the 1.68 mg/m^2 group. The event was gastrointestinal haemorrhage (1 patient), and its causal relationship to the study drug was ruled out.

7.3.10.2 Phase II

Adverse events occurred in all patients. All patients experienced an adverse event with a suspected causal relationship to the study drug. Table 34 shows adverse events with an incidence of ≥20%.

Table 34. Adverse events with an incidence of ≥20%

SOC PT (MedDRA/J ver. 16.0)	Number of patients (%) N = 50 All grades	 Grade ≥3
All adverse events	50 (100)	38 (76.0)
Infections and infestations		
Upper respiratory tract infection	16 (32.0)	0
Blood and lymphatic system disorders		
Thrombocytopenia	17 (34.0)	6 (12.0)
Neutropenia	16 (32.0)	10 (20.0)
Anaemia	10 (20.0)	2 (4.0)
Psychiatric disorders		
Insomnia	18 (36.0)	1 (2.0)
Nervous system disorders		
Neuropathy peripheral	16 (32.0)	0
Dizziness	12 (24.0)	1 (2.0)
Dysgeusia	11 (22.0)	0
Respiratory, thoracic and mediastinal disorders		
Cough	14 (28.0)	0
Gastrointestinal disorders		
Diarrhoea	29 (58.0)	5 (10.0)
Nausea	25 (50.0)	1 (2.0)
Constipation	21 (42.0)	1 (2.0)
Vomiting	16 (32.0)	1 (2.0)
Skin and subcutaneous tissue disorders		
Rash macular	10 (20.0)	1 (2.0)
Musculoskeletal and connective tissue disorders		
Back pain	17 (34.0)	3 (6.0)
Pain in extremity	11 (22.0)	1 (2.0)
General disorders and administration site conditions		
Fatigue	32 (64.0)	6 (12.0)
Oedema peripheral	19 (38.0)	2 (4.0)
Pyrexia	13 (26.0)	0

Serious adverse events were observed in 20 of 50 patients (40.0%). Serious adverse events reported by ≥2 patients were pneumonia (4 patients [8.0%]), dehydration and back pain (3 patients each [6.0%]), and diarrhoea, non-cardiac chest pain, and cardiac failure congestive (2 patients each [4.0%]). A causal relationship to the study drug could not be ruled out for pneumonia, diarrhoea, non-cardiac chest pain, and dehydration (1 patient each).

Adverse events led to discontinuation of the study drug in 4 of 50 patients (8.0%). These events were bone abscess, pneumonia respiratory syncytial viral, cardio-respiratory arrest, amnesia, peripheral sensory neuropathy, and resting tremor (1 patient each [2.0%]). A causal relationship to the study drug could not be ruled out for these events except cardio-respiratory arrest.

7.3.11 Foreign Phase I study (Study C16001)

Adverse events were observed in 115 of 116 patients (99.1%). A causal relationship to the study drug could not be ruled out events observed in 104 of 116 patients (89.7%). Adverse events with an incidence of ≥30% were fatigue (71 patients [61.2%]), thrombocytopenia (55 patients [47.4%]), vomiting (50 patients [43.1%]), decreased appetite (48 patients [41.4%]), nausea (47 patients [40.5%]), pyrexia (38 patients [32.8%]), and diarrhoea (37 patients [31.9%]).

Serious adverse events occurred in 54 of 116 patients (46.6%). Serious adverse events reported by ≥5 patients were pneumonia and thrombocytopenia (7 patients each [6.0%]) and pyrexia and dyspnoea (5 patients each [4.3%]). A causal relationship to ixazomib could not be ruled out for thrombocytopenia (7 patients), dyspnoea (2 patients), and pneumonia and pyrexia (1 patient each).

Adverse events led to discontinuation of ixazomib in 17 of 116 patients (14.7%). Adverse events leading to discontinuation of the study drug reported by ≥2 patients were pneumonia, pneumonitis, neuropathy peripheral, renal failure acute, and rash pruritic (2 patients each [1.7%]). A causal relationship to ixazomib could not be ruled out for pneumonitis, renal failure acute, and rash pruritic (2 patients each) and neuropathy peripheral (1 patient).

7.3.12 Foreign Phase I study (Study C16002)

Adverse events occurred in all patients. All patients experienced an adverse event with a suspected causal relationship to ixazomib. Adverse events with an incidence of ≥30% were fatigue (18 patients [60.0%]), diarrhoea (14 patients [46.7%]), nausea (12 patients [40.0%]), cough, thrombocytopenia, and vomiting (10 patients each [33.3%]), and headache and oedema peripheral (9 patients each [30.0%]).

Serious adverse events occurred in 10 of 30 patients (33.3%). They were pyrexia (2 patients [6.7%]) and wound infection, influenza, septic shock, mantle cell lymphoma (advanced), renal failure, renal failure acute, dyspnoea, respiratory failure, nausea, vomiting, upper respiratory tract infection, colorectal cancer, and blood creatinine increased (1 patient each [3.3%]). A causal relationship to ixazomib could not be ruled out for pyrexia, renal failure, renal failure acute, nausea, and vomiting (1 patient each).

Adverse events led to discontinuation of the study drug in 4 of 30 patients (13.3%). These adverse events were colorectal cancer, neutropenia, thrombocytopenia, asthenia, and renal failure acute (1 patient each [3.3%]). A causal relationship to ixazomib could not be ruled out for neutropenia, renal failure acute, and asthenia (1 patient each).

7.3.13 Foreign Phase I study (Study C16007)

Adverse events occurred in 26 of 27 patients (96.3%). Adverse events with a suspected causal relationship to ixazomib were observed in 22 of 27 patients (81.5%). Adverse events with an incidence of ≥30% were nausea (15 patients [55.6%]) and diarrhoea and fatigue (14 patients each [51.9%]).

Serious adverse events occurred in 15 of 27 patients (55.6%). They were pleural effusion, atrial fibrillation, and cardiac failure congestive (2 patients each [7.4%]), pain in extremity, nausea, dehydration, hypokalaemia, hyponatraemia, cholecystitis, abdominal pain, hypoxia, diarrhoea, renal failure, respiratory failure, cardiac arrest, hyperkalaemia, dyspnoea, angina pectoris, haemothorax, lobar pneumonia, fall, presyncope, hypotension, cardiac failure, facial pain, renal failure acute, and plasmacytoma (1 patient each [3.7%]). A causal relationship to ixazomib could not be ruled out for atrial fibrillation, nausea, dehydration, hypokalaemia, hyponatraemia, diarrhoea, renal failure, respiratory failure, cardiac arrest, and renal failure acute (1 patient each).

Adverse events led to discontinuation of ixazomib in 5 of 27 patients (18.5%). These adverse events were blood creatinine increased, angina pectoris, dyspnoea, respiratory failure, cardiac arrest, cardiac failure congestive, chronic renal failure, and renal failure (1 patient each [3.7%]). A causal relationship to ixazomib could not be ruled out for respiratory failure, cardiac arrest, and renal failure (1 patient each).

7.3.14 Foreign Phase I/II study (Study C16008)

Adverse events occurred in all patients. A causal relationship to the study drug could not be ruled out for events observed in 63 of 64 patients (98.4%). Adverse events with an incidence of ≥30% were oedema peripheral (36 patients [56.3%]), fatigue (35 patients [54.7%]), diarrhoea (29 patients [45.3%]), nausea (26 patients [40.6%]), constipation and insomnia (25 patients each [39.1%]), dysgeusia and neuropathy peripheral (23 patients each [35.9%]), rash maculo-papular (21 patients [32.8%]), and upper respiratory tract infection (20 patients [31.3%]).

Serious adverse events occurred in 30 of 64 patients (46.9%). Serious adverse events reported by ≥2 patients were pneumonia (4 patients [6.3%]), atrial fibrillation, lung infection, and cellulitis (2 patients each [3.1%]). A causal relationship to the study drug could not be ruled out for pneumonia (4 patients), atrial fibrillation, lung infection, and cellulitis (1 patient each).

Adverse events led to discontinuation of the study drug in 11 of 64 patients (17.2%). These adverse events were neuropathy peripheral (2 patients [3.1%]) and intestinal perforation, joint swelling, Stevens-Johnson syndrome, rash maculo-papular, oedema peripheral, Guillain-Barre syndrome, cardio-respiratory arrest, cognitive disorder, subcutaneous abscess, peripheral sensory neuropathy, and asthenia (1 patient each [1.6%]). A causal relationship to the study drug could not be ruled out for all except joint swelling, Guillain-Barre syndrome, and asthenia (1 patient each).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The assessment is ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Ninlaro has efficacy in the treatment of relapsed or refractory MM, and that the product has acceptable safety in view of its benefits. Ninlaro contains ixazomib, a new active ingredient, which binds to chymotrypsin-like activity site (β5 subunit) in 20S proteasome, a component of the ubiquitin-proteasome system, thereby inhibiting the activity of 20S proteasome. 20S proteasome inhibition is expected to induce apoptosis of tumor cells, resulting in tumor growth suppression. PMDA considers that Ninlaro has clinical significance as a treatment option for relapsed or refractory MM. The clinical positioning of ixazomib and post-marketing investigations are subject to further discussion.

PMDA has concluded that ixazomib may be approved if ixazomib is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 17, 2017

Product Submitted for Approval

Brand Name	Ninlaro Capsules 2.3 mg Ninlaro Capsules 3 mg Ninlaro Capsules 4 mg
Non-proprietary Name	Ixazomib Citrate
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	July 4, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

Following its review on Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of ixazomib citrate (hereinafter referred to as ixazomib) was demonstrated in patients with relapsed or refractory multiple myeloma (MM), by the superiority of the combination therapy with ixazomib plus lenalidomide hydrate (hereinafter referred to as lenalidomide) and dexamethasone (hereinafter referred to as DEX) to the control combination therapy with placebo plus lenalidomide and DEX in the primary endpoint, i.e., progression-free survival, in the global Phase III study (Study C16010).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

Following its review on Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events requiring particular attention during treatment with ixazomib are thrombocytopenia, gastrointestinal disorders, peripheral nerve disorder, skin disorder, infection, and posterior reversible encephalopathy syndrome.

PMDA also concluded that ixazomib should be well tolerated as long as patients are followed by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy through monitoring and control of adverse events and any other appropriate actions.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

In response to its review on Section "7.R.4 Clinical positioning" of the Review Report (1), PMDA concluded that combination therapy with ixazomib plus lenalidomide and DEX is a treatment option for Japanese patients with relapsed or refractory MM.

Also, following its review on Section "7.R.5 Indication" of the Review Report (1), PMDA concluded that ixazomib should be indicated for "relapsed or refractory MM," as proposed by the applicant. However, the "Clinical Studies" section of the package insert should note of prior treatment history, etc. of patients participated in Study C16010 along with the following statements in the "Precautions for Indications" section,.

Precautions for Indications

- Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regime.

- Eligibility of patients should be determined based on a good understanding of the data summarized in the "Clinical Studies" section of the package insert, including prior regimens of patients enrolled in the clinical studies, and the efficacy and safety of ixazomib.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to finalize the descriptions in the "Indications" and "Precautions for Indications" sections. The applicant agreed.

1.4 Dosage and administration

Following its review on Section "7.R.6 Dosage and administration" of the Review Report (1), PMDA concluded that the Dosage and Administration should be defined as "In combination with lenalidomide and dexamethasone, the usual adult dosage is 4 mg of ixazomib administered orally under fasting condition once weekly for 3 weeks (Days 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient's condition." The "Precautions for Dosage and Administration" section should give reminders to the effect of the following.

Precautions for Dosage and Administration

- The efficacy and safety of ixazomib monotherapy have not been established.

- Physicians should prescribe concomitant lenalidomide and DEX based on a thorough understanding of data provided in the "Clinical Studies" section and after careful reading of the package inserts of these concomitant drugs.

- The efficacy and safety in concomitant use of antineoplastic drugs other than lenalidomide and DEX have not been established.

- Patients with moderate or severe hepatic impairment and those with severe renal impairment are known to have increased blood ixazomib concentration. With dose reduction in consideration, patients should be closely monitored for possible adverse events.

- Postprandial doses of ixazomib are known to show decreased C_{max} and AUC. The administration of ixazomib should be refrained from 1 hour before until 2 hours after meal to avoid the effect of meals.

- The use of ixazomib should be determined based on the following criteria before the start of every treatment cycle.

Criteria for starting new treatment cycles

Neutrophil count	$\geq 1000/mm^3$
Platelet count	$\geq 75{,}000/mm^3$
Non-hematologic toxicity	Baseline level or Grade ≤1

Grading is based on NCI-CTCAE v4.0.

- In case of an ixazomib-induced adverse drug reaction, ixazomib should be suspended, discontinued, or reduced according to the following criteria.

Steps for ixazomib dose reduction

Starting dose	4 mg
Step 1 (1-level lower dose)	3 mg
Step 2 (2-level lower dose)	2.3 mg
Step 3	Discontinue

Criteria for interruption, dose reduction, and discontinuation

Adverse drug reaction	Severity	Measures taken
Thrombocytopenia	Platelet count <30,000/mm^3	Withhold ixazomib until platelet count recovers to ≥30,000/mm^3. After recovery, resume ixazomib at its most recent dose. If platelet count decreases to <30,000/mm^3 again, withhold ixazomib until it recovers to ≥30,000/mm^3. After recovery, resume ixazomib at the next lower dose.
Neutropenia	Neutrophil count <500/mm^3	Withhold ixazomib until neutrophil count recovers to ≥500/mm^3. After recovery, resume ixazomib at its most recent dose. If the count decreases to <500/mm^3 again, withhold ixazomib until it recovers to ≥500/mm^3. After recovery, resume ixazomib at the next lower dose.
Skin disorder	Grade 2	Give a symptomatic treatment for skin disorder and continue ixazomib. If the symptom is intolerable, follow "Grade 3."
	Grade 3	Withhold ixazomib until the symptom recovers to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue ixazomib.
Peripheral nerve disorder	Grade 1 with pain or Grade 2 without pain	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1 without pain. After recovery, resume ixazomib at its most recent dose.
	Grade 2 with pain or Grade 3	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue ixazomib.
Other adverse drug reactions	Grade 3 non-hematological toxicity	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4 non-hematological toxicity	Discontinue ixazomib.

Grading is based on NCI-CTCAE v4.0.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to define the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as above. The applicant agreed.

1.5 Risk management plan (draft)

In order to evaluate the safety, etc. of ixazomib in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with ixazomib, with the planned sample size of 480 patients and the follow-up period of 24 weeks (6 cycles) after the start of ixazomib administration.

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1), PMDA concluded that it is essential to conduct surveillance covering all patients treated with ixazomib for during a certain post-marketing period to collect safety data promptly in an unbiased manner and to provide available safety data to healthcare professionals without delay. Also, PMDA presented its opinions about the surveillance plan as follows.

- Key survey items should include thrombocytopenia, severe gastrointestinal disorders, peripheral nerve disorder, skin disorder, and infection.

- The target sample sizes and the follow-up period should be re-considered based on the key survey items.

The above opinions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Ixazomib, lenalidomide, and DEX are oral medications. While ixazomib is administered on Days 1, 8, and 15 of a cycle (28 days), lenalidomide is administered from Day 1 to Day 21 consecutively followed by a 7-day withdrawal period, and DEX on Days 1, 8, 15, and 22. To make clear the dosing schedule of each drug and to avoid medication errors in such complicated regimen, the applicant should prepare supporting materials for patients.

Accordingly, PMDA instructed the applicant to re-consider the surveillance plan.

The applicant's explanation:
- Thrombocytopenia, severe gastrointestinal disorders, peripheral nerve disorder, skin disorder, and infection will be added in the key survey items.
- The target sample size will be 480 patients and the follow-up period will be 6 cycles (24 weeks) after the start of ixazomib administration, based on the occurrences of events defined as the key survey items in clinical studies.
- Supporting materials will be prepared and supplied to patients for easy understanding of the dosing schedules of ixazomib, lenalidomide, and DEX.

PMDA accepted the applicant's explanation.

In view of the discussions above, PMDA has concluded that the risk management plan (draft) for ixazomib should include the safety and efficacy specifications presented in Table 35, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 36.

Table 35. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thrombocytopenia • Severe gastrointestinal disorders • Peripheral nerve disorder • Skin disorder	• Infection • Posterior reversible encephalopathy syndrome • Use in patients with renal impairment • Use in patients with hepatic impairment	• None
Efficacy specification		
• Efficacy of combination therapy with ixazomib, lenalidomide, and DEX in Japanese patients with relapsed or refractory MM		

Table 36. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance) • Post-marketing clinical study (extension of Study C16010) • Post-marketing clinical study (extension of Study C16028)	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients

Table 37. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc. of ixazomib in routine use after the market launch
Survey method	All-case surveillance
Population	All patients treated with ixazomib
Observation period	Six treatment cycles after the start of treatment with ixazomib
Planned sample size	480
Main survey items	Key survey items: Thrombocytopenia, severe gastrointestinal disorders, peripheral nerve disorder, skin disorder, and infection Other main survey items: Patient characteristics (e.g., age, sex, performance status, disease stage, concurrent illness, past illness), past treatments, information on the administration of ixazomib, concomitant drugs, adverse events, etc.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and

Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.3.3-4, 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA concluded that Ninlaro may be approved with the proposed indication and dosage and administration modified below and the conditions of approval. However, necessary precautions must be given in the package insert and post-marketing information contributing to the proper use of the product must be provided to healthcare professional. The proper use of the product must be strictly ensured under the supervision of physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy at medical institutions capable of emergency response. Because Ninlaro is an orphan drug, its re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as poisonous drugs.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

In combination with lenalidomide and dexamethasone, the usual adult dosage is 4 mg of ixazomib administered orally under fasting condition once weekly for 3 weeks (Days 1, 8, and 15), followed by a 13-day withdrawal period (Days 16-28). This 4-week treatment cycle is repeated. The dose may be reduced according to the patient's condition.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Because of limited data from Japanese clinical studies, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey should be continued until data are gathered from a certain number of patients so that the characteristics of users of the product are clearly identified and safety and efficacy data are promptly collected. The applicant should then take necessary measures to further ensure proper use of the product.

Warning

The product should be administered only to patients eligible for the treatment by a decision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy at a medical institution capable of emergency response. Prior to treatment, patients or their families should be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindications

1. Patients with a history of hypersensitivity to any ingredients of ixazomib

2. Pregnant women or women who may possibly be pregnant

Precautions for Indications

1. Ixazomib should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regime.

2. Eligibility of patients should be determined based on a good understanding of the data summarized in the "Clinical Studies" section of the package insert, including prior regimens of patients enrolled in the clinical studies, and the efficacy and safety of ixazomib.

Precautions for Dosage and Administration

1. The efficacy and safety of ixazomib monotherapy have not been established.

2. Physicians should prescribe concomitant lenalidomide and dexamethasone based on a thorough understanding of data provided in the "Clinical Studies" section and after careful reading of the package inserts of these concomitant drugs.

3. The efficacy and safety in concomitant use of antineoplastic drugs other than lenalidomide and dexamethasone have not been established.

4. Patients with moderate or severe hepatic impairment and those with severe renal impairment are known to have increased blood ixazomib concentration. With dose reduction in consideration, patients should be closely monitored for possible adverse events.

5. Postprandial doses of ixazomib are known to show decreased C_{max} and AUC. The administration of ixazomib should be refrained from 1 hour before until 2 hours after meal to avoid the effect of meals.

6. The use of ixazomib should be determined based on the following criteria before the start of every treatment cycle.

Criteria for starting a new treatment cycle

Neutrophil count	$\geq 1000/mm^3$
Platelet count	$\geq 75{,}000/mm^3$
Non-hematologic toxicity	Baseline or Grade ≤ 1

Grading is based on NCI-CTCAE v4.0.

7. In case of an ixazomib-induced adverse drug reaction, ixazomib should be interrupted or discontinued, or the dose of ixazomib should be reduced, by referring to the following criteria.

Steps for ixazomib dose reduction

Starting dose	4 mg
Step 1 (1-level lower dose)	3 mg
Step 2 (2-level lower dose)	2.3 mg
Step 3	Discontinue

Criteria for interruption, dose reduction, and discontinuation

Adverse drug reaction	Severity	Measures taken
Thrombocytopenia	Platelet count <30,000/mm^3	Withhold ixazomib until platelet count recovers to ≥30,000/mm^3. After recovery, resume ixazomib at its most recent dose. If the platelet count decreases to <30,000/mm^3 again, withhold ixazomib until it recovers to ≥30,000/mm^3. After recovery, resume ixazomib at the next lower dose.
Neutropenia	Neutrophil count <500/mm^3	Withhold ixazomib until neutrophil count recovers to ≥500/mm^3. After recovery, resume ixazomib at its most recent dose. If the count decreases to <500/mm^3 again, withhold ixazomib until it recovers to ≥500/mm^3. After recovery, resume ixazomib at the next lower dose.
Skin disorder	Grade 2	Give a symptomatic treatment for skin disorder and continue ixazomib. If the symptom is intolerable, follow “Grade 3.”
	Grade 3	Withhold ixazomib until the symptom recovers to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue ixazomib.
Peripheral nerve disorder	Grade 1 with pain, or Grade 2 without pain	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1 without pain. After recovery, resume ixazomib at its most recent dose.
	Grade 2 with pain, or Grade 3	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue treatment.
Other adverse drug reactions	Grade 3 non-hematological toxicity	Withhold ixazomib until the symptom recovers to baseline or to Grade ≤1. After recovery, resume ixazomib at the next lower dose.
	Grade 4 non-hematological toxicity	Discontinue ixazomib.

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