Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ixazomib citrate

Proprietary Product Name: Ninlaro

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

November 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au> .

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BCS	Biopharmaceutical Classification System
BD	Twice daily
BPI-SF	Brief Pain Inventory–Short Form
BSA	body surface area
CI	confidence interval
CER	clinical evaluation report
CL	clearance
C_{max}	Maximum (peak) observed plasma concentration
CNS	Central nervous system
CR	complete response
CSR	clinical study report
CTCA	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 and variants for example CYP3A4
del(17)	deletion of 17p (a portion of chromosome 17 on the short arm)
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30 MY-20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple myeloma

Abbreviation	Meaning
E-R	Exposure response
ERC_{max}	exposure ratio based on C_{max}
ESRD	end stage renal disease
FDA	Food and Drug Administration
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GLP	Good laboratory practice
hERG	Human ether-a-go-go-related gene
HR	Hazard ratio
IC50	concentration producing 50% inhibition
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMiD	immunomodulatory drugs
IRC	independent review committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous; intravenously
Km	Michaelis constant
K-M	Kaplan-Meier
Len/Dex	lenalidomide and dexamethasone
LSM	least square mean
MATE	multi-antimicrobial extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRP2	Multidrug resistance-associated protein 2

Abbreviation	Meaning
MSC	Mesenchymal stem cells
MTD	maximum tolerated dose
NCA	non-compartmental analysis
NDMM	newly diagnosed multiple myeloma
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOEL	No observable effect level
NTCP	Na^+ taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptide
OCT2	Organic Cation Transporter 2
ORR	overall response rate
OS	overall survival
PCM	plasma cell malignancy
PD	progressive disease
PFS	progression-free survival
PhV	pharmacovigilance
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRO	patient-reported outcome
PSC	pharmaceutical subcommittee
PT	preferred term
QoL	quality of life
QTc	rate-corrected QT interval (millisecond) of electrocardiograph
RMP	Risk Management Plan
RRMM	relapsed and/or refractory multiple myeloma
RSE	Relative standard error

Abbreviation	Meaning
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplant
SJS	Stevens-Johnson Syndrome
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SOC	system organ class
t½	terminal disposition phase half-life
TEAE	Treatment emergent adverse event
TEN	Toxic Epidermal Necrolysis
T_{max}	first time of occurrence of maximum(peak) observed plasma concentration
TNF-α	Tumour necrosis factor alpha
ULN	upper limit of the normal range
US	United States
Vd	Volume of distribution
VGPR	very good partial response

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 November 2016
Date of entry onto ARTG	15 November 2016
Active ingredient:	Ixazomib (as citrate)
Product name:	Ninlaro
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd GPO Box 2728 Sydney NSW 2001
Dose form:	capsule
Strengths:	2.3 mg, 3 mg and 4 mg
Container:	Blister pack
Pack sizes:	1 and 3 capsules
Approved therapeutic use:	*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*
Routes) of administration:	oral
Dosage:	4 mg, orally once a week on days 1, 8 and 15 of a 28 day treatment cycle; used in combination with lenalidomide and dexamethasone. For full details please see the product information (PI).
ARTG numbers:	260934, 260935 and 260936

Product background

This AusPAR describes the application by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Ninlaro ixazomib (as citrate) 2.3 mg, 3 mg and 4 mg capsules for oral administration for the following indication:

> *'Ninlaro is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.'*

Treatment options for patients with relapsed or refractory multiple myeloma (RRMM) have increased with the availability of thalidomide, lenalidomide, bortezomib, and pomalidomide based regimens in addition to chemotherapy protocols. Regimens for the treatment of RRMM including thalidomide and its derivatives been incorporated into the

most recent clinical practice guidelines of the Myeloma Foundation of Australia (2015), however, these guidelines precede the registration of bortezomib.[1] For patients with RRMM, entry into clinical trials remains a primary management decision, given the ongoing poor outcome for these patients. The use of thalidomide or lenalidomide is limited by the occurrence of peripheral neuropathy and risk of thromboembolism.

Ixazomib is an oral, selective and reversible proteasome inhibitor. Ixazomib preferentialIy binds and inhibits the chymotrypsin like activity of the beta 5 subunit of the 20S proteasome. Ixazomib demonstrated in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines.

Ixazomib citrate is the citrate ester of the biologically active dipeptide boronic acid (ixazomib). Ixazomib citrate drug substance is a pro-drug that rapidly hydrolyses under physiological conditions to ixazomib, its biologically active form.

The recommended starting dose of Ninlaro is 4 mg (one capsule) administered orally once a week on Days I, 8, and 15 of a 28 day treatment cycle.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 November 2016.

At the time the TGA considered this application, a similar application had been approved in:

- USA; approved 20 November 2015: 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
- Venuzuela (MSP); approved 16 May 2016 for: Ninlaro is indicated for the treatment of patients with Multiple Myeloma who have received at least one prior therapy
- Canada; approved 4 August 2016 for 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.
- Israel; approved 14 August 2016 for the same indications as USA.
- European Union; CHMP positive opinion 15 September 2016 for the same indications as Canada.

and was under consideration in Switzerland (submitted 24 September 2015) and Singapore (submitted 10 March 2016). The sponsor stated that the product was also under review by an additional 8 health authorities (details not provided).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .:

II. Quality findings

Introduction

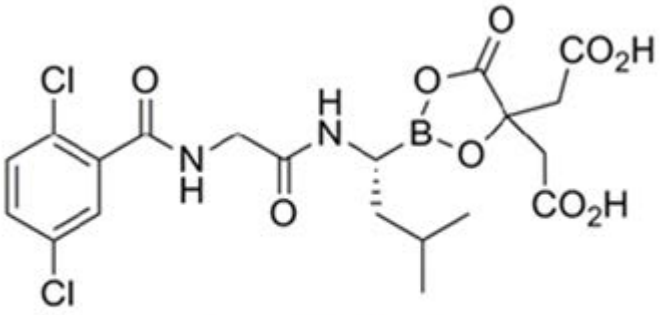
Ixazomib is a new chemical entity which inhibits the chymotrypsin like activity of the 20S proteasome subunit beta-5. Takeda Pharmaceuticals Australia Pty Ltd has applied to register Ninlaro ixazomib capsules for use in the treatment of multiple myeloma, in combination with lenalidomide and dexamethasone.

Drug substance (active ingredient)

Ixazomib is synthetic boronic acid [that is R-B(OH)2]; the structure is shown in Figure 1. The drug substance used is the citric ester: 2-[(1R)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diacetic acid. The company code for ixazomib is MLN9708.

Ixazomib has one chiral centre; the drug substance is as a single stereoisomer (R configuration). There is no evidence of racemisation during processing or storage.

Figure 1: Structure of ixazomib citrate



ixazomib citrate

ixazomib $C_{14}H_{19}BCl_2N_2O_4$ MW 361

ixazomib citrate $C_{14}H_{17}BCl_2N_2O_4.C_6H_6O_5$ MW 517

In keeping with modern practice, the capsule label claim is the amount of the active moiety, here ixazomib. Ixazomib citrate hydrolyses in water, for example in vivo, to the ixazomib (boronic acid) form as shown in Figure 2.

Figure 2: Hydrolysis of Ixazomib citrate to ixazomib (boronic acid) form

The drug substance is white crystalline solid (melting point 231°C). Solubility is higher at neutral pH, but solubility is high relative to the proposed dose at all physiological pH. Particle size is weakly controlled, but dissolution is not strongly dependent on it.

Impurity levels are low. The enantiomer is controlled. The drug substance is stored at 5°C.

Drug product

Takeda seeks to register Ninlaro ixazomib 2.3 mg, 3 mg and 4 mg hard gelatin capsules. Excipients are conventional. The different strengths are not scaled, but the different formulation ratios are very unlikely to affect bioavailability.

The non-proportional set of strengths (2.3, 3.0, 4.0 mg) proposed correspond to 3.29, 4.30 and 5.73 mg ixazomib citrate. The recommended starting dose is 4 mg (one capsule) administered orally once a week on days 1, 8, and 15 of a 28 day cycle.

The strengths are well distinguished by different capsule colours and markings ('2.3 mg', '3.0 mg', '4.0 mg' and Takeda logo). Single capsule PVC+Al / Al blisters are packed in cartons (total of 3 capsules per carton).

Routine in vitro dissolution testing of capsule batches uses a basket apparatus at 100 rpm with 500 mL of 0.1N HCl.

Levels of free ixazomib have been tested during development but remain low.

Capsules are stored below 30°C. Stability is somewhat affected by water levels, with low levels of boron and amide cleavage (both hydrolytic and oxidative). Pharmaceutical aspects are considered acceptable.

Biopharmaceutics

Bioavailability

Ixazomib citrate is Class III (high solubility, low permeability) according to the Biopharmaceutical Classification System (BCS). Given the BCS class III for ixazomib, similarity in the different strengths of the commercial formulations and the dissolution performance of the 2.3 mg and 4 mg capsules, the bioequivalence of the different strengths of capsules is considered established.

Peak plasma levels of ixazomib occur approximately 1 hour after dosing and the absolute bioavailability is reported as 58%. Due to the cytotoxicity of ixazomib a traditional cross over absolute bioavailability study was not conducted. Instead the absolute oral bioavailability of ixazomib was estimated using population pharmacokinetic analysis. Co-administration with food significantly reduces bioavailability by 28% in Study C16009.

Cytochrome P450 (CYP) enzyme metabolism was detectable only at high concentrations and included 3A4, 2B6, 1A2 and other enzymes to lesser extents. Volume of distribution (Vd) was reported as 543 L at steady state with extensive distribution into red blood cells (area under the plasma concentration versus time curve (AUC) ratio plasma to red cells 1: 10).

Ixazomib is excreted as metabolites mostly in urine (62%) with 22% in faeces.

Kinetics was reported to be linear over the dose range 0.2 to 10.6 mg.

Biopharmaceutic aspects are acceptable

Advisory committee considerations

The dosage form is conventional and no unusual aspects have arisen in review of the chemistry or biopharmaceutic aspects, thus, in keeping with current policy, it is not planned to refer the submission to the pharmaceutical subcommittee (PSC).

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

Ninlaro is proposed to be used for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. The proposed dosing regimen involves oral administration of one capsule (4 mg ixazomib) on days 1, 8, and 15 of a 28 day cycle at least 1 hour before or at least 2 hour after food. The draft Product Information (PI) document indicates that Ninlaro is to be used in combination with lenalidomide (25 mg on days 1 to 21 of a 28 day cycle) and dexamethasone (40 mg on days 1, 8, 15 and 22 of a 28 day cycle)

Ixazomib has a similar pharmacological target to bortezomib; both are proteasome inhibitors, acting on the 20S proteasome chymotryptic activity.

The submitted nonclinical dossier was in accordance with the International Conference on Harmonisation (ICH) guideline[1] and was considered acceptable. No notable deficiencies were observed, though the assessment for off-target effects was limited.

Pharmacology

Primary pharmacology

In vitro studies

Ixazomib was developed to have the same mode of action as bortezomib. In vitro, ixazomib was a reversible inhibitor of 20S proteasome activity, preferentially targeting the β5 site (associated with chymotrypsin like activity) (concentration producing 50% inhibition (IC50) 3.4 nM; approximately 3 times the clinical free maximum (peak) observed plasma concentration (C_{max})) with 10 to 1000 fold lower potency at the β1 (caspase like) and β2 (trypsin like) sites and even lower potency at a number of serine and cysteine proteases (including chymotrypsin). In cells, ixazomib inhibited proteasome activity (IC50 9.7 nM; approximately10 times the clinical free C_{max}) and NF-κB[2] activation by TNF-α[3] (IC50 55 nM). The IC50 values for ixazomib were approximately1.5 to 3 fold higher than those for bortezomib. Ixazomib induced apoptosis in cultured multiple myeloma (MM) cell lines (EC50 approximately25 nM) and reduced the viability of MM cells obtained from patients (at 50 nM) after multiple prior therapies including bortezomib, lenalidomide and dexamethasone. Higher concentrations were required to overcome the proliferative advantage conferred by micro-environmental cells (Mesenchymal stem cells (MSCs) or osteoclasts). In vitro studies indicated ixazomib suppressed osteoclastogenesis, inhibited osteoclast resorption and promoted osteogenic differentiation and matrix mineralisation of osteoprogenitor cells from patients with

[1] ICH harmonised tripartite guideline on the nonclinical evaluation of anticancer pharmaceuticals (ICH S9).
[2] NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival.
[3] Tumour necrosis factor alpha is a cell signalling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction

myeloma. Ixazomib was reported to be more active than bortezomib against bortezomib resistant MM cells in vitro (IC50 ratio resistant/sensitive approximately2.3 fold for ixazomib compared with approximately5.5 for bortezomib; actual IC50 values not reported).[4] The combination of ixazomib with lenalidomide had synergistic effects on the viability of cultured MM cells. The in vitro data support the proposed use of ixazomib with lenalidomide for the treatment of patients with MM, and for the most part, the proposed dose.

Ixazomib had similar potency at the 20S proteasome in monkey and human blood, but slightly lower potency in rat and dog blood (1.3 to 3.5 times lower). However, there was no significant difference in IC50 values in plasma from rats, monkeys and humans. The animal and human data are considered sufficiently similar to support the use of rats and dogs in the general toxicity studies.

In vivo studies

Ixazomib (given via either the intravenous (IV) or oral (PO) routes) was tested for anti-tumour activity in mice bearing human MM xenografts and mouse models of plasma cell malignancy (PCM) that demonstrate features of human MM (the iMycCα/Bcl-XL model of de novo PCM, and disseminated and intratibial models of PCM). Ixazomib (not the citrate salt) was used in the studies. In a mouse MM model, an IV or PO dose resulted in high ixazomib levels in tumours and inhibition of 20S proteasome 5β site and increased cleaved caspase-3 (an apoptosis marker). Tumour growth was inhibited by > 90% at oral doses ≥ 6 mg/kg given twice weekly for 18 days (plasma C_{max} and AUC at 6 mg/kg approximately15 and 5 times the respective clinical values). Doses (IV) given once weekly were as efficacious as a similar dose given twice weekly. Ixazomib treatment prevented tumour associated bone loss in a disseminated murine model of human myeloma. The animal studies support the proposed clinical indication, although the efficacious dose in the mouse models was higher than the proposed clinical dose.

No animal studies were conducted to assess the efficacy of co-administration with lenalidomide or dexamethasone. No animal studies were conducted to assess efficacy in models that were resistant to other treatments (for example, bortezomib). No studies assessing possible resistance mechanisms were submitted.

Secondary pharmacodynamics and safety pharmacology

Ixazomib (at 10 μM; 10,000 times the clinical free C_{max}) had no significant inhibitory activity at 14 neurotransmitter related receptors, 3 ion channels and brain/gut peptide receptor. The set of off target sites examined is limited. A broader range of off target sites should have been included in the assessment.

Dedicated safety pharmacology studies covered the cardiovascular system. Effects on the central nervous and respiratory systems were examined in repeat dose toxicity studies. In vitro, there was no clinically relevant inhibition of human ether-a-go-go-related gene (hERG) K^+ tail current (IC50 59.6 μM; > 50,000 times the clinical free C_{max}). No abnormalities in electrocardiogram (ECG) parameters were evident in dogs treated with ≤ 0.21 mg/kg PO ixazomib citrate (approximately11 times the clinical C_{max}) or ≤ 0.15 mg/kg IV ixazomib citrate[5] (resulting in 15 times the clinical C_{max}). There was no evidence of an effect on respiratory function in rats treated with ≤ 0.3 mg/kg IV ixazomib citrate and dogs treated with ≤ 0.15 mg/kg IV ixazomib citrate (resulting exposures 8 and

[4] Chauhan D et al. (2011) *In vitro* and *in vivo* selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells*. Clin. Cancer Res*. 2011; 17: 5311-5321.
[5] Repeat-dose toxicity study WIL-416107, C_{max} 538 ng/mL.

15 times the clinical C_{max}, respectively). No adverse effects on cardiovascular or respiratory function are predicted in patients.

There was limited evidence of effects on central nervous system (CNS) function in rats dosed with ≤ 0.3 mg/kg IV (exposure ratio based on C_{max} (ERC_{max}) 9). At higher doses (and higher peak plasma levels), hypoactivity was observed, but as the doses exceeded the maximum tolerated dose (MTD), it is uncertain if the hypoactivity is associated with a direct effect on CNS function. After single IV doses of ≥ 0.3 mg/kg ixazomib (ERC_{max} 7), lethargy and ataxia were observed in dogs (no observable effect level (NOEL) 0.1 mg/kg IV; ERC_{max} 4). With repeated dosing, degeneration of neuronal tissues (in both the central and peripheral nervous systems) was observed at very low exposures and was often evident in the absence of overt clinical signs of nervous system effects. This neuropathy has been observed with bortezomib (including the species differences in sensitivity observed with ixazomib) and is discussed further in the repeat dose toxicity section.

Pharmacokinetics

The rate of oral absorption[6] was rapid in rats, dogs and humans (first time of occurrence of maximum (peak) observed plasma concentration (T_{max}) ≤ 1 hour) and much slower in rabbits (T_{max} 24 hours). Bioavailability by the oral route was low to moderate in rats, rabbits and humans (19 to 58%) and very high in dogs (approximately100%). In vitro studies indicated that ixazomib had moderate permeability, and while it was a low affinity substrate for efflux transporters (P-glycoprotein, breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2); efflux ratio ≤ 3 and Km 239 µM compared with estimated intestinal concentration of 44 µM ixazomib at the proposed dose of 4 mg), the transporters are expected to have a minor impact on the oral absorption of ixazomib. Following IV dosing to rats, rabbits, dogs and monkeys, plasma half-lives were very long (32 hours to 9.5 days) with low to moderate clearance. There were no obvious sex differences in pharmacokinetic parameters in either rats or dogs. There was no consistent evidence of accumulation in rats following twice weekly dosing; however, there seemed to be some evidence for accumulation in dogs following daily or twice weekly dosing.

Plasma protein binding by ixazomib was high to very high in humans and laboratory animal species and concentration dependent (92 to 96% in animal species and 88% in human plasma in vitro at 2 µM and approximately99% ex vivo with plasma samples from patients treated with ixazomib). Binding in human plasma was largely attributable to albumin. The distribution of ixazomib into blood cells from mice, rats, dogs, monkeys and humans was high with an apparent inverse relationship with concentration (blood:plasma ratio 1 to 10 at 1 to 0.1 µg/mL). Red blood cells are known to contain high concentrations of 20S proteasome.[7] The volume of distribution was larger than total body water in rats, rabbits, dogs, monkeys and humans, suggesting extensive extravascular distribution. Consistent with this, tissue distribution of radioactivity in rats after IV or PO administration of radiolabelled ixazomib or ixazomib citrate was rapid and wide. Tissues with concentrations (C_{max} or AUC) higher than those in blood, included tissues involved in absorption/excretion (GI tract, kidney, liver), adrenal gland, bone marrow, lymph node, pituitary gland, salivary gland, spleen, thymus and thyroid. There appeared to be some retention of radioactivity in male reproductive organs, resulting in exposures higher than those seen in blood. There also appeared to be some retention of radioactivity in the

[6] As ixazomib citrate is hydrolysed rapidly to ixazomib, the pharmacokinetics of ixazomib are considered to be similar if provided as ixazomib or ixazomib citrate.
[7] Neelam S, et al. (2011) Functional 20S proteasomes in mature human red blood cells. *Experimental Biology & Medicine* 2011; 236: 580-591.

sciatic nerve (terminal disposition phase half-life (t½) was 5 times that in blood). There was no specific affinity or retention of radioactivity in melanin-containing tissues. In a dedicated study in rats, concentrations of drug related material in the dorsal root ganglion were similar to those in blood. Exposures in the brain were 11 to 12% those in blood.

Ixazomib citrate was rapidly (non-enzymatically) hydrolysed to ixazomib. Metabolism of ixazomib (in vitro and in vivo) involved oxidative deboronation, other oxidation, dehydrogenation, N-dealkylation, hydrolytic and conjugation reactions. Metabolites observed in in vitro incubations with hepatocytes and microsomes were different from those observed in vivo in rats, dogs and humans. Based on in vitro studies, the metabolism of ixazomib appeared to involve largely non-cytochrome P450 (CYP450) mediated pathways, though CYP3A4 and CYP1A2 appear to have minor roles in ixazomib metabolism. There were no unique human metabolites. Ixazomib was the predominant circulating drug related compound in all species.

Excretion of ixazomib and/or its metabolites was predominantly via the faeces in rats and urine in humans, while both the faecal and urinary routes contributed to the excretion of drug related material in dogs. Biliary excretion was demonstrated in rats. An in vitro study with sandwich-cultured hepatocytes indicates a low potential for biliary excretion of ixazomib in human subjects.

Aside from a slight difference in the excretion pattern of drug related material, the pharmacokinetic profile of ixazomib citrate was qualitatively similar in humans and the species used in toxicity studies (rats and dogs) and they are considered adequate to serve as appropriate models for toxicity.

Pharmacokinetic drug interactions

As CYP450s only play a minor role in the metabolism of ixazomib citrate, inhibitors of CYP450 enzymes are not expected to significantly alter the pharmacokinetics of ixazomib. As CYP3A4 and 1A2 have a minor role in the metabolism of ixazomib, inducers of these CYPs may increase the contribution of CYP450s to the clearance of ixazomib. The draft Product Information document indicates that strong CYP3A inducers decrease ixazomib exposures. There was no clinically relevant inhibitory activity on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 enzyme activity in human liver microsomes. Ixazomib (citrate) was not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5. There was no significant induction of CYP1A2, 2B6 or 3A4/5 enzyme activity or protein levels in human hepatocytes in response to ixazomib citrate treatment.

Ixazomib was a low affinity substrate for P-glycoprotein, BCRP and MRP2. Inhibitors of these transporters are not expected to significantly alter the plasma kinetics of ixazomib. Ixazomib (citrate) was not a substrate for organic anion-transporting polypeptide (OATP) transporters or Na^+ taurocholate co-transporting polypeptide (NTCP). Ixazomib (citrate) had no clinically relevant inhibition of P-glycoprotein (P-gp), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, Organic Cation Transporter 2 (OCT2), multi-antimicrobial extrusion protein (MATE) MATE1 or MATE2K transport.

In conclusion, pharmacokinetic drug interactions involving transporters are not predicted. Ixazomib citrate is not expected to alter exposures to CYP450 substrates. Based on clinical data, strong CYP3A4 inducers may reduce ixazomib exposures. It is noted that lenalidomide is not an inducer of CYP450 enzymes (Revlimid PI).

Toxicology

Acute toxicity

Single dose toxicity studies were conducted with ixazomib following PO and IV dosing to rats and IV dosing to dogs. None of the studies were conducted under good laboratory practice (GLP) conditions and only an 8 day observation period was used. No target organs for toxicity were identified in rats, while the GI tract and nervous system were target organs for toxicity in dogs. The maximum non-lethal oral dose was the highest dose tested in rats (1 mg/kg; estimated ERC_{max} 1.5[8]), while the maximum non-lethal IV dose was 0.3 mg/kg in rats and 0.1 mg/kg in dogs (ERC_{max} 3 to 5), indicating a high order of acute toxicity.

Repeat dose toxicity

Fourteen repeat dose toxicity studies in rats and dogs were submitted. The test item was either ixazomib citrate or its hydrolysis product, ixazomib. The dosing route was either via the clinical route (PO) or via the IV route. The toxicity was generally similar regardless of test item or dosing route. The duration of the longest studies (pivotal studies; approximately6 months in rats and approximately9 months in dogs), is considered appropriate given the indication. The choice of species (rat as the rodent and dog as the non-rodent species) is considered acceptable.

The dosing regimen in the pivotal studies (once per week for 3 weeks of a 28 day cycle) is consistent with that proposed for clinical use. The dosing regimen used in the remaining GLP studies consisted of twice weekly dosing for 2 weeks to approximately3 months by the PO or IV route, with each cycle separated by a 10 day non dosing period, and provided additional toxicological data.

Relative exposure

Exposure ratios have been calculated based on weekly exposures (that is animal: human plasma $AUC_{0-168\,h}$). The AUC data used for animals is the mean of male and female values on the last sampling occasion. The studies in which dosing was twice weekly, the AUC_{0-24h} was multiplied by two to equate to a weekly exposure. Exposures were generally subclinical in rats, while exposures up to only 4 fold the clinical exposure were achieved in dogs. Given the low margins, the toxicities below should all be considered as potentially clinically relevant.

Table 1: Relative exposure in repeat dose toxicity studies with ixazomib citrate

Species	Study duration [Study no.]	Dose (mg/kg)	AUC0–168 h^ (ng·h/mL)	Exposure ratio#
Rat(Sprague Dawley)	5 cycles[a] **IV** [Study WIL-416106] *(twice weekly dosing)*	0.05	368	0.3
		0.15	908	0.8
		0.3	1884	1.7
	5 cycles[a] **PO** [Study WIL-416104] *(twice weekly dosing)*	0.2	311	0.3
		0.4	505	0.5
		0.8→0.6	592	0.5
	7 cycles (6 months)[b] **PO** [Study WIL-416165] *(once weekly dosing)*	0.2	483	0.4
		0.4	779	0.7
		0.8→0.6	1135	1.1

[8] Based on data in Study RPT-01130 (Day 1 data).

Species	Study duration [Study no.]	Dose (mg/kg)	AUC0–168 h^ (ng·h/mL)	Exposure ratio#
Dog (Beagle)	5 cycles[a] **IV** [Study WIL-416107] *(twice weekly dosing)*	0.05	1376	1.3
		0.1	2760	2.6
		0.15	2940	2.7
	5 cycles[a] **PO** [Study WIL-416105] *(twice weekly dosing)*	0.05	776	0.7
		0.1	1499	1.4
		0.15	2524	2
	10 cycles (9 months)[b] **PO** [Study WIL-416164] *(once weekly dosing)*	0.05	934	0.9
		0.1	1940	2
		0.2	3900	4
Human (patients)	steady state	[4 mg]	1080	–

= animal: human plasma $AUC_{0-168\ h}$; ^ = data are for both sexes combined at the last sampling occasion; [a] Each cycle consisted of twice weekly dosing for 2 weeks, with each cycle separated by a 10 day non-dosing period (20 day cycle); [b] Each cycle consisted of 3 once weekly doses separated by 13 days of non-dosing (28 day cycle)

Major toxicities

The toxicity profile of ixazomib citrate was similar to that of bortezomib. The target organs for toxicity were the GI tract, lymphoid tissues, bone marrow and peripheral and central nervous systems.

Gastrointestinal disturbances (including soft faeces, diarrhoea and, in dogs, vomiting) were accompanied by epithelial degeneration and mucosal inflammation (epithelial hyperplasia, single cell necrosis, increased incidence of neutrophil infiltrates) of intestines and stomach/glandular stomach. The findings were similar following oral or IV dosing, suggesting the effects are not simply caused by local irritation. The GIT effects were reversible.

Bone marrow hypocellularity and lymphoid depletion and/or necrosis in the lymph node, spleen, thymus and Peyer's patches were evident in both species. Haematological changes (anaemia, thrombocytopaenia, eosinopaenia) were occasionally observed and likely secondary to bone marrow changes. However, in longer term studies, increased levels of circulating neutrophils and monocytes were seen in both species, suggestive of an inflammatory response. All of these findings were seen in toxicity studies conducted with bortezomib, and the effects were reversible.

Neuronal degeneration and degeneration of peripheral nerve fibres were routinely observed in treated dogs by PO or IV administration. Dogs appeared to be more sensitive to these effects as chromatolysis of the dorsal root ganglion was only observed in rats following IV administration. These effects had not fully reversed after a 2 week treatment-free period and after 5 weeks in dogs receiving 4 IV doses at 0.18 mg/kg twice weekly (exposure approximately 22 times the clinical exposure based on C_{max}, and approximately2 times the clinical exposure based on AUC). It is unclear if a full reversal would have been seen with a longer duration recovery period. These degenerative changes were not always accompanied by overt clinical signs. There was no evidence of functional deficits in the 9 month dog study, where neuronal function tests were conducted. However, as with bortezomib, peripheral neuropathy and some sensory effects may be seen in patients, particularly when used in conjunction with lenalidomide, which is also known to cause peripheral neuropathy in some patients.

Hepatic toxicity was evident in rats only at high PO or IV doses, exhibited as single hepatocyte necrosis, hepatocellular degeneration/hypertrophy/vacuolation, increased

liver weight, and in some cases, small increases in plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT). There was no evidence of liver toxicity in dogs.

In the 6 month rat study, increased mucin was seen in the mandibular salivary glands. This was not observed in any other study (either species). The clinical relevance of this singular finding is unknown.

Overall, the toxicity profile of ixazomib is similar to bortezomib, with GI disturbances, peripheral neuropathy, and haematological changes (as a result of bone marrow depression, inflammation and lymphoid depletion) predicted in patients.

No studies were conducted to assess the toxicity of ixazomib citrate with lenalidomide or dexamethasone. Bortezomib is currently approved for use with thalidomide and dexamethasone. The toxicities observed with that combination may be expected with an ixazomib-lenalidomide-dexamethasone combination.

Genotoxicity

The genotoxic potential of ixazomib was assessed in a bacterial mutagenesis assay, while ixazomib citrate was assessed in the in vitro clastogenicity study in human peripheral blood lymphocytes, mouse micronucleus study and Comet assay in mice. All assays were appropriately validated and conducted under GLP conditions. Ixazomib was not mutagenic to bacterial cells. Positive results were observed in the in vitro clastogenicity assay (± S9, generally at concentrations resulting in ≥ 50% reduction in mitotic index), but negative results were observed in the two in vivo studies (with doses resulting in exposures [C_{max}] up to 22 times the C_{max} observed in patients). The overall weight of evidence would indicate that ixazomib is not genotoxic. The genotoxicity study results are similar to the findings for bortezomib (that is positive clastogenicity at high concentrations in vitro, but negative results in vivo).

Carcinogenicity

No carcinogenicity studies were submitted, which is considered acceptable given the indication.[1]

Reproductive toxicity

Reproductive toxicity studies were restricted to effects on embryofetal development in rats and rabbits. The lack of fertility and postnatal development studies is considered acceptable given the indication.[1] The test item was ixazomib citrate, provided by the clinical route (PO). Dosing in the animal studies was more frequent than the proposed clinical dosing regimen (every 3 days compared with once weekly). Adequate animal numbers were used with doses in the pivotal studies selected following the outcome of dose ranging studies. Exposure ratios were determined based on both AUC (2 x AUC_{0-72h} to estimate an AUC_{0-168h} in animals) and C_{max}, as adverse embryofetal development effects can be associated with exposures on a single day. Exposures in animals ranged from subclinical to marginally greater than the clinical exposure, therefore all effects reported below should be considered as potentially clinically relevant.

Table 2: Relative exposure in reproductive toxicity studies with ixazomib citrate

Species	Study [Study no.]	Dose (mg/kg every 3 days; PO)	$AUC_{0-168\ h}$ (ng·h/mL)	C_{max} (ng/mL)	Exposure ratio based on	
					AUC	C_{max}
Rat (SD)	Embryofetal development [Study	0.2	978	12	0.9	0.3
		0.4	1476	33	1.4	0.9
		0.6	2206	49	2.0	1.3

Species	Study [Study no.]	Dose (mg/kg [illegible])	$AUC_{0-168\ h}$ (ng·h/m[illegible])	C_{max} (ng/mL)	Exposure ratio based on	
	MLN9708-26378]					
Rabbit (NZW)	Embryofetal development [Study MLN9708-28154]	0.1	994	9	0.9	0.2
		0.3	1584	15	1.5	0.4
		1	2628	29	2.4	0.8
Human (patients)	steady state	[4 mg]	1080	37	–	–

In both rats (at 0.6 mg/kg every 3 days) and rabbits (1 mg/kg every 3 days), there was an increased incidence of post-implantation loss. There was no evidence of teratogenicity or fetal anomalies in rats. In rabbits, there was an increased incidence of fetal skeletal abnormalities/variations (shortened tail, unossified caudal vertebra, fused caudal vertebra, full supernumerary rib and variation in the number of lumbar vertebrae) at 0.3 and/or 1 mg/kg every 3 days. Exposures at the NOAEL for embryofetal toxicity were similar to (based on AUC) or below (based on C_{max}) the clinical exposure. All of the adverse embryofetal development effects occurred at maternotoxic doses; however, a direct drug related effect cannot be completely dismissed. The extent of placental transfer of ixazomib is unknown, but if sufficient transfer occurred, ixazomib has the potential to disrupt protein cycling in the developing fetus and, therefore, may have an adverse effect on fetal development.

Pregnancy classification

The sponsor has proposed Pregnancy Category C[9]. This category is for drugs, which owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. Given the potential for ixazomib to have adverse effects on fetal development based on its pharmacological activity, Pregnancy Category C is considered appropriate. This is the same Pregnancy Category as bortezomib.

Immunotoxicity

No specific immunotoxicity studies were submitted. The bone marrow and lymphoid tissues were target organs for toxicity in the repeat dose studies and are likely to be affected in human subjects. It is unknown what effects these may have on immunocompetence.

Phototoxicity

In a tissue distribution study in rats, there was no indication of specific affinity or retention of drug related material to melanin. Ixazomib citrate was not phototoxic in vitro to cultured cells. Ixazomib citrate is not considered to pose a phototoxic risk.

Impurities

The proposed limits for specified impurities/degradants in the drug substance/drug product are at or below the applicable qualification thresholds. A number of compounds that are used as starting materials, arise as process intermediates or are potential

[9] Pregnancy Category C is defined as: *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

impurities were identified by structural alert analyses to be potentially mutagenic. Given the infrequent treatment regimen and life expectancy of the patient population, no toxicological qualification is required for the impurities.

Paediatric use

Ixazomib citrate is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline.[1] The overall quality of the nonclinical dossier was reasonable. All pivotal safety related studies were GLP compliant. No notable deficiencies were observed, though the assessment for off-target effects was limited.
- In vitro, ixazomib was a reversible inhibitor of 20S proteasome activity, preferentially targeting the β5 site. Ixazomib induced apoptosis in cultured MM cell lines and reduced the viability of MM cells obtained from patients after multiple prior therapies including bortezomib, lenalidomide and dexamethasone. The combination of ixazomib with lenalidomide had synergistic effects on the viability of cultured MM cells. In vivo, ixazomib treatment inhibited tumour growth and prevented tumour-associated bone loss in murine models of human myeloma. The animal studies support the proposed clinical dose and generally support the proposed dosing regimen.
- No animal studies were conducted to assess the efficacy of co-administration with lenalidomide or dexamethasone.
- No significant inhibitory activity was observed at 14 neurotransmitter related receptors, 3 ion channels and brain/gut peptide receptor. A broader range of off-target sites should have been included in the assessment.
- No adverse effects were seen on cardiovascular function in dogs, or respiratory function in rats and dogs. No adverse effects on cardiovascular or respiratory function are predicted in patients. With repeated dosing to dogs, degeneration of neuronal tissues (in both the central and peripheral nervous systems) was observed at very low exposures and was sometimes accompanied by overt clinical signs of nervous system effects.
- Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Ixazomib was rapidly absorbed with a similar T_{max} in all species. Half-life values were very long. Plasma protein binding of ixazomib was high to very high in all animal species and humans. Excretion of ixazomib and/or its metabolites was predominantly via the faeces in rats and urine in humans, while both the faecal and urinary routes contributed to the excretion of drug related material in dogs. Biliary excretion was demonstrated in rats.
- Pharmacokinetic drug interactions involving transporters are not predicted. Ixazomib citrate is not expected to alter exposures to CYP450 substrates. Inhibitors of CYP450 enzymes are not expected to significantly alter the pharmacokinetics of ixazomib. As CYP3A4 and 1A2 have a minor role in the metabolism of ixazomib, inducers of these CYPs may increase the contribution of CYP450s to the clearance of ixazomib.
- Ixazomib had a high order of acute oral toxicity in rats and dogs.

- Repeat dose toxicity studies were conducted in rats (up to 6 months) and dogs (up to 9 months). Maximum exposures (AUC) were low. The toxicity profile of ixazomib citrate was similar to that of bortezomib. The target organs for toxicity were the GI tract (including soft faeces, diarrhoea and, in dogs, vomiting; degenerative changes in the stomach/glandular stomach, epithelial hyperplasia and inflammation), lymphoid tissues (lymphoid depletion and/or necrosis), bone marrow (hypocellularity) and peripheral and central nervous systems (neuronal and peripheral nerve fibre degeneration).
- Ixazomib was not mutagenic. Positive results were observed in an in vitro clastogenicity assay, but negative results were observed in two in vivo studies (mouse micronucleus study and Comet assay). The overall weight of evidence would indicate that ixazomib is not genotoxic. No carcinogenicity studies were conducted, which is considered acceptable.
- Reproductive toxicity studies examined effects on embryofetal development toxicity in rats and rabbits. An increased incidence of postimplantation loss was observed in both species. There was no evidence of teratogenicity or fetal anomalies in rats. In rabbits, there was an increased incidence of fetal skeletal abnormalities/variations. All of the adverse embryofetal development effects occurred at maternotoxic doses (resulting in exposures similar to or slightly exceeding the clinical exposure); however, a direct drug related effect cannot be completely dismissed.

Conclusions and recommendation

- The primary pharmacology studies lend some support for the proposed indication.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
  - Gastrointestinal disturbances
  - Peripheral neuropathy
  - Reduced immunity as a result of lymphoid depletion
  - Possible alterations in haematological parameters
- The safety of the combination of ixazomib citrate with lenalidomide and dexamethasone has not been assessed in submitted nonclinical studies. Provided adequate clinical safety data are available for the combination use, there are no objections on nonclinical grounds to the registration of ixazomib citrate for the proposed indication.

The nonclinical evaluator also made recommendations relating to the PI and the nonclinical safety specification of the Risk Management Plan (RMP) however these are beyond the scope of the AusPAR

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The clinical rationale for the development of ixazomib was based on multiple myeloma (MM) being an incurable disease and the inevitability of relapse after available first line

therapies. While bortezomib based therapies are frequently the preferred choice of treatment for relapse following previous treatment, "*a new generation proteasome inhibitor is required to improve clinical outcomes with greater efficacy, less toxicity, and greater patient convenience*" (for example, ixazomib). Multiple myeloma remains a disease of high clinical unmet need.

The latest updated edition of the Clinical Practice Guideline Multiple Myeloma (August 2015; V.3), co-ordinated on behalf of the Medical Scientific Advisory Group (MSAG) of the Myeloma Foundation of Australia (MFA), states that, "*despite improved therapies, MM remains an incurable disease [with] approximately one third of patients not responding to front-line therapy, and eventual relapse occurring in virtually all patients who obtain an initial response*". The guidelines indicate that the "*main treatment options for relapsed/resistant disease are newer agents (thalidomide, bortezomib, lenalidomide and pomalidomide), alkylating agents, anthracyclines, bendamustine and corticosteroids administered alone or in various combinations, with selected patients undergoing high dose therapy (HDT) with autologous stem cell transplant (AuSCT)*". The guideline notes that, while various agents can be used in different combinations and sequences for relapsed/resistant disease, no best sequence has been defined.

Ixazomib was initially formulated for intravenous (IV) use and subsequently for oral (PO) use as immediate release capsules.

Contents of the clinical dossier

The submission contained the following clinical information:

- 12 dedicated clinical pharmacology studies
- 2 population pharmacokinetic analyses (1 preliminary, 1 final)
- 1 pivotal Phase III efficacy and safety Study C16010
- 2 Phase I, single agent, dose finding studies (C16004, C16003)
- 1 exposure response report; 1 integrated safety summary; 1 severe cutaneous adverse event report; 1 ad hoc analysis based on 262 progression free survival (PFS) events; 1 safety summary in special populations; literature references
- 23 in vitro bioanalytical reports; 2 in vitro plasma protein binding studies
- Clinical Overview; Summary of Biopharmaceutics; Summary of Clinical Efficacy; Summary of Clinical Pharmacy; Summary of Clinical Safety; tabular summary of studies; literature references.

Paediatric data

The submission did not include paediatric data. The sponsor has a waiver from having to present a Paediatric Investigation Plan (PIP) in Europe. The sponsor states that MM is currently on the list of paediatric class waivers published by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). Confirmation that ixazomib for treatment of RRMM falls under this class waiver was received by the sponsor from the EMA on 12 April 2013 (EMA/143949/2013). The sponsor has a waiver from the US FDA from having to submit a Paediatric Assessment. The waiver is based on US legislative provisions which exempt drugs with an orphan designation from the requirement to submit paediatric studies.

Comment: The sponsor's decision not to submit paediatric data to the TGA is considered to be acceptable. The proposed indication relating to patients with RRMM who

have previously been treated with at least one prior therapy is likely to occur almost exclusively in adults.

Good clinical practice

The sponsor states that the clinical studies were conducted in accordance with good clinical practice (GCP), according to the International Conference on Harmonisation (ICH) final guideline (01 May 1996).

Pharmacokinetics

Studies providing pharmacokinetic data

A total of 14 clinical studies have contributed to the characterisation of the clinical pharmacology of ixazomib in this submission.

All studies were conducted in patients with cancer, including MM (RRMM and newly diagnosed multiple myeloma (NDMM)) and other advanced haematological and non-haematological malignancies. In total, clinical pharmacokinetic data were available from the 14 studies on approximately 990 patients of both sexes, with a median age of approximately 66 years. Blood samples (rich or sparse sampling) were collected in each study for assessment of pharmacokinetic (PK) endpoints.

The PK data in the individual study reports were calculated from plasma, whole blood or urinary concentrations of ixazomib using standard non-compartmental analysis (NCA). Tabulated summaries of the 14 PK studies were provided. In addition to the PK data from the individual studies, the submission also included a population pharmacokinetic (PPK) report performed using PK data from 755 patients (108 IV; 647 PO) from 10 clinical PK studies. All individual clinical pharmacology reports were of high quality, as were the two PPK analyses (initial and updated). The approach to the evaluation of the PK data has been to include all relevant data in the body of the clinical evaluation report (CER; please see Attachment 2). The 14 individual studies contributing PK data are summarised below in Table 3.

Table 3: Clinical studies contributing to the clinical pharmacology of ixazomib included in the submission

Study Number	Phase	Formulation	Clinical Pharmacology Objectives
IV Studies			
C16001	1	Intravenous – Solution	Characterize the PK and pharmacodynamics
C16002	1	Intravenous – Solution and Lyophilized Powder for Solution	Characterize the PK and pharmacodynamics
Oral, Single Agent			
C16003, C16004	1	Oral Capsule – Formulation A	Characterize the PK
C16007	1	Oral Capsule – Formulation B	Characterize the PK
Oral, Combination with Lenalidomide and Dexamethasone			
C16005, C16008	1/2	Oral Capsule – Formulation B	Characterize the PK
C16010	3	Oral Capsule – Formulation B	Population PK and exposure-response analysis
DDI, Food Effect and Relative Bioavailability			
C16009	1	Oral Capsule – Formulation A (Arm 2[a]) Formulation B (Arms 1 to 5)	Relative bioavailability of 2 capsule formulations, DDI (strong CYP3A inhibitors or inducers), food effect
Mass Balance/ADME			
C16016	1	Oral Solution – (^{14}C-ixazomib)[a] Oral Capsule – Formulation B	Radiolabeled mass balance/ADME study
Special Populations			
C16015	1b	Oral Capsule – Formulation B	Effect of severe renal impairment including ESRD patients requiring hemodialysis on PK
C16018	1	Oral Capsule – Formulation B	Effect of moderate or severe hepatic impairment on PK
Asian Populations			
C16013	1	Oral Capsule – Formulation B	Characterize the PK in Asian patients
TB-MC010034	1	Oral Capsule – Formulation B	Characterize the PK in Japanese patients

ADME=absorption, distribution, metabolism, and excretion; DDI=drug-drug interactions; PK=pharmacokinetics.
(a) PK cycle only.

Population pharmacokinetics

The submission included two PPK Reports. The reporting of the results of the two PPK analyses was consistent with the TGA adopted EMA guidance document.[10]

The first PPK analysis (preliminary PPK analysis report) was conducted using data from the first 4 clinical Studies C16001, C16002, C16003 and C16004, in order to evaluate the possibility of switching from a body surface area (BSA) based dosing regimen to a fixed dose regimen. Data were pooled from 226 adult patients with MM, lymphoma, or solid tumours from the four Phase I clinical studies which used BSA based ixazomib dosing (PO or IV, once or twice weekly). The preliminary population PK modelling was undertaken using NONMEM version 7.2. The final report for this analysis was dated 21 May 2015.

The Final PPK Report (MIL-PKPD-MLN9708-021), dated 22 May 2015, superseded the preliminary PPK Report. The PPK data summarised in this CER are from the final report. The Final PPK Report included data from seven Phase I Studies C16001, C16002, C16003, C16004, C16007, C16013, and TB-MC010034, two Phase I/II Studies C16005, and C16008,

[10] CHMP/EWP/185990/06 , 21 June 2007 Guideline on reporting the results of population pharmacokinetic analyses

and one Phase III Study C16010. The pooled PPK analysis dataset, including data from 755 patients (108 IV; 647 PO), was constructed based on data from all ten trials. Patients were treated with BSA adjusted ixazomib doses in Studies C16001, C16002, C16003, C16004, and C16005 (Phase 1 part), and fixed ixazomib doses in Studies C16005 (Phase 2 part), C16007, C16008, C16010, C16013, and TB-MC010034. Treatment with ixazomib was administered weekly (Days 1, 8 and 15 of a 28 day cycle) or twice weekly (Days 1, 4, 8 and 11 of a 21 day cycle). The final dataset for the PPK analysis is summarised below in Table 4, and the studies contributing to the Final PPK Report.

Table 4: Final PPK Report - Data included in the analysis set

Study ID	Number of patients	Number of PK samples	Number of dose records
C16001	80	1017	295
C16002	28	579	80
C16003	52	934	203
C16004	51	841	139
C16005	62	644	305
C16007	15	176	43
C16008	63	691	435
C16010	347	3871	7554
C16013	43	859	117
TB-MC010034	14	295	38
Total	755	9907	9209

Evaluator's conclusions on pharmacokinetics

- The PK of ixazomib have been adequately characterised in 14 clinical studies with clinical pharmacology data and in the Final PPK Report. All PK data were from patients with cancer.
- The proposed ixazomib oral formulation is an immediate release capsule. It is administered as a stable citrate ester and the conversion of ixazomib citrate in plasma to ixazomib is reported to be immediate and complete. Based on Biopharmaceutical Classification System (BCS) criteria, ixazomib is categorised as a Class 3 compound (that is, high solubility, low permeability). Absorption following oral administration of ixazomib was rapid, with T_{max} values of approximately 1 hour being consistently observed across studies when the drug was administered in the fasting state.
- Based on the final PPK analysis, the observed ixazomib IV and oral plasma concentration data were adequately described by a three compartment model with linear distribution and elimination kinetics, including first order linear absorption with lag time describing the oral dose PK profile. The ixazomib plasma concentration time profile was multi exponential after both IV and PO dosing.
- The absolute bioavailability of ixazomib is estimated to be 58% (relative standard error (RSE): 9%), based on PPK data from 10 clinical studies (108 IV; 647 PO). No dedicated absolute bioavailability study was submitted. However, the sponsor justified the absence of such a study in accordance with the ARGPM, Guidance 15.[information redacted] Overall, it is considered that the sponsor's justification for not submitting a dedicated absolute bioavailability is acceptable.
- The submission included a relative bioavailability Study C16009, Arm 2 comparing the two ixazomib 4 mg capsule formulations (A and B) used in the clinical development program. Formulation A was used in the first two oral Phase I studies

and formulation B was used in all 9 subsequent oral Phase I/II studies and in the one pivotal oral Phase III study. In Study C16009 (Arm 2), both formulations A and B (single dose) were bioequivalent based on the 90% CI of the $AUC_{(0\text{-}216h)}$ ratio (B/A), which was within the accepted interval of 0.80 to 1.25 (that is, geometric least square mean (LSM) ratio = 1.04 [90% CI: 0.91, 1.18]) However, the 90% CI of the C_{max} ratio (B/A) was not enclosed entirely within the accepted interval of 0.80 to 1.25 (that is, geometric LSM ratio = 1.16 [0.84, 1.61]). The median T_{max} values of the two formulations were similar (that is, 1.3 hours). In addition, the mean plasma concentration time profiles of the two formulations over the first 216 hours after administration demonstrated similar disposition of ixazomib over this time period. Overall, the two formulations are considered to have similar systemic exposures, but cannot be categorised as bioequivalent due to the difference in the C_{max} values.

- The submission included a food effect Study C16009, Arm 3 comparing the bioavailability of ixazomib (4 mg capsule, formulation B, single dose) administered in the fasting and the fed states. Exposure to ixazomib was significantly reduced when it was administered with a high fat meal, with reductions of 28% in the $AUC_{(0\text{-}216h)}$ and 69% in the C_{max}. In addition, the median T_{max} was delayed by approximately 3 hours in the fed state (that is, increasing from 1 hour fasting to 4 hours fed). The results indicate that ixazomib should be administered without food. The proposed PI recommends that ixazomib should be taken at the same time on days 1, 8, and 15 at least 1 hour before or at least 2 hours after food.
- The pivotal Phase III study was conducted with capsule formulation B, which is the capsule formulation proposed for registration. Consequently, no bioequivalence study comparing the oral formulation used in the pivotal Phase III study with the proposed oral commercial formulation was required.
- The steady state volume of distribution is estimated to be 543 L (final PPK analysis). The volume of distribution is large, indicating that ixazomib is extensively distributed to the extravascular tissues. Ixazomib is highly bound (99%) to plasma proteins (predominantly serum albumin) and the extent of binding is not altered by severe renal impairment Study C16015 or moderate or severe hepatic impairment Study C16018. Ixazomib concentrations were higher on Day 15 in whole blood than in plasma, with blood-to-plasma ratios for C_{max} and $AUC_{(0\text{-}168h)}$ of 2.89 and 9.86, respectively Study C16007. The data suggest extensive partitioning of ixazomib into red blood cells, possibly due to binding to 20S proteasomes reportedly found in high concentrations in red blood cells.
- The systemic clearance of ixazomib was estimated to be 1.86 L/hr (relative standard error (RSE) = 7%), based on the final PPK analysis. The geometric mean estimate for the terminal half-life was 9.5 days (95% CI: 9.32, 9.75 days), based on the final PPK analysis. Ixazomib is a low clearance drug (based on a plasma clearance of 1.86 L/hour and a blood/plasma ratio of approximately 10), which appears to account for the prolonged terminal half-life of the drug. There was an approximately 2 fold accumulation of ixazomib (based on AUC) following the Day 15 dose for the proposed 4 mg once weekly schedule (Days 1, 8, and 15). Trough ixazomib concentrations suggest that steady state is not achieved within the first cycle of either the once weekly or twice weekly ixazomib dosing regimen.
- Based on the estimated absolute bioavailability of 58% and the systemic clearance of 1.86 L derived from the final PPK analysis, it can be calculated that the apparent oral clearance (CL/F) of ixazomib is 3.21 L/hr. The geometric mean renal clearance of ixazomib is 0.119 L/hour (Study C16016), which is 3.7% of the estimated apparent oral clearance of 3.21 L/hr, suggesting that renal clearance does not meaningfully contribute to ixazomib clearance in humans.

- As indicated above, metabolism appears to be the major route of elimination of ixazomib. In vitro studies suggest that ixazomib is metabolised by multiple cytochrome P450 (CYP) and non-CYP proteins. It was reported that at supra-therapeutic concentrations of ixazomib (10 μM), which were > 90 fold higher than the geometric mean clinically relevant C_{max} (0.11 μM), ixazomib was metabolised in vitro by multiple CYP isoforms, with estimated relative contributions for 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), CYP2C19 (4.8%), and 2C9 (< 1%). However, at more clinically relevant concentrations of ixazomib (0.1 and 0.5 μM), it was reported that non-CYP proteins seemed to have a major role in ixazomib clearance in vitro.
- In vitro, ixazomib was reported to be neither a time dependent inhibitor nor a reversible inhibitor of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. In addition, ixazomib was reported in vitro not to induce CYP 1A2, 2B6, or 3A4 activity or corresponding immunoreactive protein levels. Consequently, based on the in vitro data it can be reasonably inferred that the potential for ixazomib to produce significant drug-drug interactions via CYP isozyme induction or inhibition is low.
- In vitro, ixazomib was reported to be a low affinity substrate of P-gp, with P-gp mediated ixazomib transport accounting for 19% of the total transport of the drug in Caco-2 cells. In vitro, ixazomib was reported not to be a substrate for BCRP, MRP2 and OATPs, or an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Consequently, based on the in vitro data it can be reasonably inferred that ixazomib is unlikely to cause or be susceptible to clinically significant drug-drug interactions with substrates or inhibitors of drug transporters.
- The mass balance (ADME) clinical study showed that approximately 62% of the administered radioactivity was recovered in the urine and 22% was recovered in the faeces. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged drug collected up to 168 hours after oral dosing, suggesting that renal elimination is a minor clearance pathway for ixazomib and that most of the total radioactivity in urine was attributable to metabolites of ixazomib.
- In clinical Study C16009, co-administration of ixazomib with the strong CYP3A4 inhibitor clarithromycin did not result in a clinically meaningful increase in ixazomib exposure. The geometric LSM ratios for the C_{max} and $AUC_{(0\text{-}264h)}$ were 0.96 (90% CI: 0.67, 1.36) and 1.11 (90% CI: 0.86, 1.43), respectively. The analysis compared data for ixazomib alone (2.5 mg, single dose) from patients treated on C1D1 in Arm 1, and for ixazomib (2.5 mg, single dose) administered on Day 6 after 5 days of repeat dosing with clarithromycin (500 mg -BD with clarithromycin continuing from Day 6 through 16 of C1 in Arm 5. This design was adopted in order to avoid the period effect observed in Arm 1, where ixazomib exposure in Period 2 (ixazomib co-administered with ketoconazole) might have been confounded by the fixed-sequence design in which ixazomib alone had been administered in Period 1. The ixazomib concentration in Period 2 might have been confounded due to an ixazomib carry over effect from Period 1 due to an inadequate wash-out between the two periods resulting from the long terminal half-life of the drug.
- The 2.5 mg dose of ixazomib used in Study C16009 investigating the effect of co-administration ixazomib and clarithromycin was lower than the proposed starting dose of 4 mg. On the basis of in vitro drug metabolism data and the contribution of renal clearance to the elimination of the drug, a less than 2 fold increase was expected in ixazomib systemic exposure (AUC) with strong CYP3A inhibition. Therefore, the 2.5 mg dose was anticipated to provide an adequate margin of safety for conduct of the drug-drug interaction studies with ketoconazole and clarithromycin, as ixazomib exposures during co-administration with these

inhibitors were anticipated to be less than those observed at the MTD of 5.5 mg that had been estimated in an earlier clinical pharmacology study in patients with RRMM (Study C16004). In addition, the reduced 2.5 mg dose of ixazomib (relative to the Phase III clinical dose of 4 mg) was considered appropriate for evaluation of exposure when co-administered with strong CYP3A inhibitors, on the basis of dose linear PK of ixazomib. Overall, the DDI data indicate that no ixazomib dosage adjustment is required when co-administered with strong CYP3A4 inhibitors.

- In clinical Study C16009, a clinically meaningful reduction in ixazomib exposure was observed when co-administered with the strong CYP3A4 inducer rifampin. When co-administered with rifampin, the $AUC_{(0\text{-last})}$ was reduced by 74% (that is, geometric LSM ratio = 0.26 [90% CI: 0.18, 0.37]) and the C_{max} was reduced by 54% (that is, geometric LSM ratio = 0.46 [90% 0.29, 0.73]). The results of this clinical DDI study indicate that ixazomib should not be co-administered with strong CYP3A4 inducers.
- In the PPK analysis, the effect of smoking status on the PK of ixazomib was assessed. It was inferred that PK differences between smokers and non-smokers would be due to induction of CYP1A2 metabolic activity in smokers. In the PPK analysis, smoking status was not identified as a significant covariate on the PK of ixazomib (that is, clearance, absolute oral bioavailability, or the volume of the second peripheral compartment). In addition, based on the final PPK model the predicted percent decrease in median ixazomib AUC_{inf} for patients who were current smokers compared to patients who had never smoked was 8% (95% CI: -23, 9). The magnitude of the difference (8%) in AUC_{inf} between patients who self-identified as current smokers and patients who had never smoked was < 20%, suggesting no clinically meaningful difference in exposures between the two groups. However, it is important to note that the smoking history was self-reported. Based on the results of the PPK analysis, no ixazomib dosage adjustment is required when co-administered with CYP1A2 inducers.
- In the PPK analysis, the effect of strong CYP1A2 inhibitors (ciprofloxacin) on the PK of ixazomib was examined as a time dependent categorical covariate. No significant effects of strong CYP1A2 inhibitors on ixazomib clearance could be identified. The PPK model estimated a 9% higher median ixazomib AUC_{inf} (95% CI: 6, 12%) for patients receiving strong CYP1A2 inhibitors compared to those not receiving strong CYP1A2 inhibitors. The magnitude of the difference (9%) in AUC_{inf} between the two treatment groups was < 20%, suggesting no clinically meaningful difference in exposures between the two groups. The data suggest that no dose adjustment is necessary for ixazomib when co-administered with strong CYP 1A2 inhibitors.
- In the PPK analysis, the effect of Len/Dex co-administered with ixazomib was assessed. Based on the final PPK model, Len/Dex co-administered with ixazomib was not identified as a statistically significant covariate on ixazomib clearance, absolute oral bioavailability, or the volume of the second peripheral compartment. In addition, based on the final PPK model the predicted percent decrease in median ixazomib AUC_{inf} for ixazomib co-administered with Len/Dex compared to ixazomib administered alone was 7% (95% CI: 0, 17). The magnitude of the difference (7%) in AUC_{inf} between the two treatment groups was < 20%, suggesting no clinically meaningful difference in exposures. There were no data on the effect of ixazomib on the PK of Len.
- The effect of severe renal impairment was investigated in a dedicated Study C16015. In patients with severe renal impairment (including patients with end stage renal disease (ESRD), the unbound $AUC_{(0\text{-last})}$ increased by 38% (that is, geometric LSM ratio = 1.38 [90% CI: 0.93, 2.04]) and the unbound C_{max} increased

by 25% (that is, geometric LSM ratio = 1.25 [90% CI: 0.79, 1.98]) compared to patients with normal renal function. The results indicate that a lower starting dose of ixazomib 3 mg in patients with severe renal impairment should result in similar ixazomib exposure to a higher starting dose of ixazomib 4 mg in patients with normal renal function. Study C16015 also showed that ixazomib was not dialysable in patients with end stage renal disease (ESRD) requiring haemodialysis.

- The effect of moderate or severe hepatic impairment on the PK of ixazomib was investigated in a dedicated Study C16018. In this study, the effects of moderate and severe hepatic impairment on the PK of ixazomib were similar. In patients with moderate/severe hepatic impairment, the unbound dose normalised $AUC_{(0\text{-last})}$ increased by 27% (geometric LSM ratio = 1.27 [90% CI: 0.75, 2.16]) and the unbound dose normalised C_{max} increased by 24% (that is, geometric LSM ratio = 1.24 [90% CI: 0.79, 1.95]) compared to patients with normal hepatic function. The results indicate that a lower starting dose of ixazomib 3 mg in patients with severe or moderate hepatic impairment should result in similar ixazomib exposure to a higher starting dose of ixazomib 4 mg in patients with normal hepatic function.
- The PPK analysis showed that covariates of age, sex, or race had no significant effects on the PK of ixazomib, and that the predicted effects on AUC_{inf} were unlikely to be clinically meaningful. The only covariate included in the final model was BSA on V4, and inclusion of BSA explained 12.6% of the variability on V4. Patients at the 5th and 95th percentiles of BSA were predicted to have a 37% lower and a 46% higher V4, respectively, than the median patient. However, BSA does not affect exposure (AUC_{inf}), as BSA was not identified as a covariate on CL.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included the following studies providing pharmacodynamic data:

- 2 Phase I Studies C16001 and C16002 investigating the effect of ixazomib IV on 20S proteasome inhibition;
- 1 study (Millennium-A2PG-0001 Report) investigating the effects of ixazomib on rate-corrected QT interval (millisecond) of electrocardiograph (QTc) prolongation;
- 1 Exposure response analysis investigating the relationship between ixazomib exposure and clinical response; and
- 1 Exposure safety analysis investigating the relationship between ixazomib exposure and selected treatment emergent adverse events (TEAEs).

Evaluator's conclusions on pharmacodynamics

- The data from the Phase I Studies C16001 and C16002 showed that the maximum tolerated doses of IV ixazomib reversibly inhibited 20S proteasome activity. Maximal inhibition of 20S proteasome inhibition occurred within 30 minutes of IV administration, indicating a close temporal association between maximum pharmacodynamic effect and maximum plasma concentration.
- The Millennium-A2PG-0001 Report demonstrated no clinically meaningful differences between the placebo and ixazomib regimens in the incidence of QTc prolongation. Neither regimen appears to be associated with clinically significant effects on QTc prolongation. The pooled data from the analysis indicate that the risk of pro-arrhythmia associated with ixazomib is low. Model predictions of mean

ΔΔQTcF[11] at the geometric mean of C_{max} (48 ng/mL) for a 4 mg single dose were 0.07 msec (90% CI: -0.22, 0.36 msec). The upper limit of the 90% CI was well below 5 msec.

- The exposure response (E-R) analyses demonstrated that ixazomib exposure was not a significant predictor of clinical responses (complete response (CR)), ≥ very good partial response (VGPR), ≥ partial response (PR)) and was not a significant predictor of PFS.
- The E-R analyses demonstrated a significant relationship ($p < 0.05$) between ixazomib exposure and selected treatment emergent adverse events (TEAEs) (rash, peripheral neuropathy, diarrhoea, nausea, vomiting, fatigue, thrombocytopenia, and anaemia).

Dosage selection for the pivotal studies

The submission included one pivotal Phase III Study C16010. In this study, the starting dose of ixazomib was 4 mg administered on Days 1, 8, and 15 of a 28 day cycle in combination with Len/Dex regimen. The proposed dosing regimen was supported by nonclinical data and clinical trial results in which ixazomib was administered as a single agent and in combination with the Len/Dex.

Comment: Based on the data from the combination Study C16005 and the two single agent Studies C16003 and C16004, it is considered that the sponsor's decision to assess the efficacy of ixazomib 4 mg once weekly on Days 1, 8 and 15 of a 28 day cycle in combination with Len/Dex in the pivotal Phase III Study C16010 is appropriate. The TEAEs observed in Study C16005 were generally manageable with dose modification (that is, reduction, temporarily holding) and/or standard supportive care. The types of TEAEs observed were generally expected on the basis of clinical experience with the first in class proteasome inhibitor, Velcade, and clinical experience with the Len/Dex background regimen.

Efficacy

Studies providing efficacy data

Pivotal efficacy Study C16010

Supportive efficacy studies: Study C16003 (Phase I) and Study C16004 (Phase I), in a total of 120 patients (intent to treat (ITT) population) with RRMM, as supportive efficacy studies (n = 60 in each of the two studies).

For the full clinical evaluation of efficacy please see Attachment 2.

Evaluator's conclusions on efficacy

For the full clinical evaluator's conclusion on efficacy please see Attachment 2.

[11] ΔΔQTcF = placebo corrected, change from baseline predicted QT interval after correction for heart rate (Fridericia's correction); relative to concentration of 0

Overall conclusion

On balance, it is considered that the efficacy data from Study C16010 are sufficiently robust to support approval of the proposed ixazomib regimen for the treatment of patients with RRMM whose disease has progressed on at least one prior therapy.

Safety

Studies providing safety data

Two routes of administration have been evaluated in the ixazomib clinical development program; an IV route (2 studies) and an oral route (18 studies). The total number of patients enrolled in the ixazomib clinical trials with safety data was 1,622 (990 [oral studies] + 146 [IV studies] + 486 [studies contributing death and serious adverse event (SAE) listings, but not integrated into the overall safety analysis population]). The safety data for 5 patients enrolled in the mass balance study were not included in the International Staging System (ISS) as the ixazomib oral solution was radiolabelled. The studies contributing patients to the safety assessment are summarised in Table 5 (oral) and Table 6 (IV).

Table 5: Safety population, dosing schedule and accrual status of oral ixazomib studies

Indication	Patient Population	Study Number	Safety Population	Dosing Schedule (combination)	Accrual Status[a]	Included in Integrated Summary of Safety
Multiple Myeloma	Newly Diagnosed	C16005	65	Phase 1/2 weekly+LenDex	Closed	✓
		C16008	64	Phase 1/2 twice weekly+LenDex		✓
		C16006	61	Phase 1/2 weekly or twice weekly+MP		✓
		C16014	276	Phase 3 weekly+LenDex vs Placebo+LenDex	Enrolling	✓ Not integrated[b]
		C16019	11	Phase 3 weekly vs Placebo Maintenance after ASCT		✓ Not integrated[b]
	Newly Diagnosed & Relapsed/ Refractory	C16020	34	Phase 2 weekly+CD		✓
	Relapsed/ Refractory	C16003	60	Phase 1 twice weekly	Closed	✓
		C16004	60	Phase 1 weekly		✓
		C16010[c]	360 placebo 360 ixazomib	Phase 3 weekly+LenDex vs Placebo+LenDex		✓
		C16010[c] China Continuation	38	Phase 3 weekly +LenDex vs Placebo+LenDex	Enrolling	✓ Not integrated[b]
		C16013	43	Phase 1 weekly +LenDex in Asia	Closed	✓
		TB-MC010034	14	Phase 1 weekly single-agent or +LenDex in Japanese patients	Closed	✓
		C16015	30	Phase 1 Renal impairment weekly+Dex	Enrolling	✓
AL Amyloidosis		C16007	27	Phase 1 weekly	Closed	✓
		C16011	30	Phase 3 weekly +Dex vs Physician's choice	Enrolling	✓
Solid Tumors	Advanced Solid Tumors	C16009	93	Phase 1 DDI, FE, relative BA		✓
		C16016[d]	4	Phase 1 mass balance, PK, metabolism, and elimination		✓ Not integrated
		C16018	41	Phase 1 Hepatic impairment weekly		✓
Lymphoma	Advanced Follicular Lymphoma	C16017	10	Phase 2 weekly		✓

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; AL= systemic light-chain; ASCT= autologous stem cell transplant; BA=bioavailability; CD=cyclophosphamide and dexamethasone; DDI=drug-drug interaction; Dex=dexamethasone; FE=food effect; LenDex=lenalidomide and dexamethasone; MP=melphalan and prednisone.

a Accrual status as of data cut-off (30 October 2014 [C16010] and 02 October 2014 [for all other ongoing studies and the respective database lock dates for those studies which were completed by 02 October 2014]).

b Only deaths and serious adverse event line listings included in summary of safety; these are not integrated.

c Although Study C16010 (global) and C16010 China Continuation are included under the same protocol number, the database and analysis of C16010 China Continuation data are separate from the database and analysis of C16010 (global). Data from C16010 China Continuation are not included in the integrated safety analysis, as the targeted number of events for unblinded analysis has not been met.

d Data for the 4 patients enrolled in Study C16016 at the time of the data cut-off are not integrated in this Summary of Clinical Safety because of the radioactive ([^{14}C]-ixazomib) component in the oral solution; the safety data are summarized in a clinical study report (see Section 5.11.1).

Table 6: Safety population, dosing schedule and accrual status of IV ixazomib studies

Indication	Study Number	Safety Population	Dosing Schedule (combination)	Accrual Status	Included in Summary of Safety
Advanced lymphomas	C16002	30	Phase 1 weekly	Closed	Separate pooled IV analysis
Advanced solid tumors	C16001	116	Phase 1 twice weekly		

Evaluator's conclusions on safety

It is considered that the safety of the proposed ixazomib regimen for the treatment of the proposed patient population has been satisfactorily established by the safety data from the pivotal Phase III Study C16010, supported by the safety data from the overall safety analysis population in which ixazomib was administered as a single agent or part of a combined regimen for various conditions including, but not limited to MM.

In general, the safety profile of the ixazomib regimen (n = 360) in the pivotal Study C16010 in patients with RRMM was consistent with the safety profile of ixazomib in patients included in the overall safety analysis population (n = 990), of whom 80% had a diagnoses of MM (RRMM or NDMM). The 990 patients in the overall safety analysis population treated with ixazomib included 360 (36%) patients from the ixazomib regimen in the pivotal study. Based on the "rule of threes" and a patient population of 360 exposed to the proposed ixazomib regimen in the pivotal study, adverse drug reactions to the proposed regimen with a frequency of greater than or equal to 1 in 120 (that is, approximately ≤ 1%) can be reasonably excluded.

In the pivotal study, the safety population included 720 patients, comprising 360 patients each in the proposed ixazomib plus Len/Dex regimen (the ixazomib regimen) and the placebo plus Len/Dex regimen (the placebo regimen). The duration of exposure was similar for the two treatment regimens and, consequently, the TEAE rates did not have to have to be adjusted to account for differences in exposure. The median number of treatment cycles was 13.0 (range: 1, 26) in the ixazomib regimen and 12.0 (range: 1, 25) in the placebo regimen. The median duration of treatment was similar in the ixazomib and placebo regimens (340.5 and 334.0 days, respectively). Overall, 296 (82%) patients in the ixazomib regimen and 298 (83%) patients in the placebo regimen received at least 6 cycles, while 215 (60%) patients in the ixazomib regimen and 205 (57%) patients in the placebo regimen received at least 12 cycles. The median dose intensity was 97.4% for ixazomib and 98.2% for placebo. There were 271 (75%), 148 (41%), 45 (13%), and no patients treated with ixazomib for ≥ 6, ≥ 12, ≥ 18 and ≥ 24 months, respectively. There were 199 (55%) patients in the ixazomib regimen still on treatment at the data cut-off date compared to 188 (52%) patients in the placebo regimen.

The overall safety analysis population included 990 patients exposed to at least 1 dose of oral ixazomib (either as a single agent or in combination with other chemotherapeutic regimens, regardless of patient population) from Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16010, C16011, C16013, C16015, C16017, C16018, C16020, and TB-MC010034. The median number of ixazomib treatment cycles was 7.0 (range: 1, 69 cycles). Overall, 153 patients (15%) received at least 18 cycles of ixazomib, while 58 patients (6%) received at least 24 cycles of ixazomib. The maximum number of cycles of ixazomib was 69 (approximately 4 years). The median dose intensity of ixazomib was 96.2%. There were 483 (49%), 241 (24%), 105 (11%), and 32 (3%) patients treated with ixazomib for ≥ 6, ≥ 12, ≥ 18 and ≥ 24 months, respectively.

In general, the incidence of categorised TEAEs was similar in the ixazomib and placebo regimens in the pivotal study. The categorised TEAEs in which there were greater than 5% more patients in the ixazomib regimen compared to the placebo regimen were Grade ≥ 3 TEAEs (68% versus 61%, respectively), drug regimen-related Grade ≥ 3 TEAEs (54% versus 46%), TEAEs resulting in dose modification of 1 or more of the 3 agents in the study regimen (71% versus 64%), and TEAEs resulting in dose reduction of 1 or more of the 3 agents in the study regimen (52% versus 44%). The incidence of the following TEAE categories was similar in patients in the ixazomib and placebo regimens (< 5% difference), all TEAEs (98% versus 99%, respectively), drug regimen-related TEAEs (91% versus 88%, respectively), SAEs (40% versus 44%, respectively), drug related SAEs (23% each regimen), TEAEs resulting in discontinuation of 1 or more of the 3 agents in the study regimen (19% versus 17%, respectively), TEAEs resulting in discontinuation of the full drug regimen (13% versus 11%, respectively), and on-study deaths (3% versus 5%, respectively). Overall, the results suggest that the increased toxicity in the ixazomib regimen compared to the placebo regimen is manageable by dose reductions rather than treatment discontinuation.

The sponsor nominated a number of TEAEs as being of clinical importance, based on preferred terms (PTs) or pooled PTs depending on the events. The TEAEs of clinical

importance were heart failure, arrhythmias, myocardial infarction, rash, nausea, vomiting, diarrhoea, thrombocytopenia, neutropenia, liver impairment, peripheral neuropathy, encephalopathy, renal impairment, and hypotension. In the pivotal Study C16010, TEAEs of clinical importance reported in ≥ 5% more patients in the ixazomib regimen compared to the placebo regimen were diarrhoea (PT: 42% versus 36%), rash (pooled PTs: 35% versus 21%), thrombocytopenia (pooled PTs: 28% versus 14%), peripheral neuropathy (pooled PTs: 28% versus 21%), nausea (PT: 26% versus 21%), and vomiting (PT: 22% versus 11%). There was < 5% difference in the percentage of patients for all other TEAEs of clinical importance, namely, heart failure (pooled PTs), arrhythmias (pooled PTs), myocardial infarction (pooled PTs), neutropenia (pooled PTs), liver impairment (pooled PTs), encephalopathy (pooled PTs), renal impairment (pooled PTs), and hypotension (pooled PTs).

The major limitation of the safety data in the pivotal Study C16010 relates to the relatively small number of patients treated for ≥ 12 months (that is, 148 [41%] patients). This is a limitation as the sponsor is proposing no time limit on the duration of treatment. Therefore, in the absence of disease progression and adverse events continued treatment with the regimen for the proposed indication can be anticipated. However, some reassurance comes from the long-term data from the pivotal study that showed that the incidence of most TEAE categories declined with continued exposure in patients who had completed ≥ 12 cycles. In addition, dose modifications of ixazomib specifically due to TEAEs were more common in Cycles 1 to 6 and decreased in frequency over time. Furthermore, in the overall safety analysis population, 241 (24%) of the 990 patients were treated with ixazomib for ≥ 12 months, 105 (11%) patients for ≥ 18 months, and 32 (3%) patients for ≥ 24 months. Similar to the findings in the pivotal study, the incidence of TEAEs in the overall safety analysis population decreased over time. Overall, the available data relating to prolonged administration suggest that long-term treatment with the proposed ixazomib regimen will be reasonably well tolerated and that cumulative toxicity is unlikely to occur. However, the occurrence of an increased number of new primary malignancies is a potential concern associated with long-term treatment with the proposed ixazomib regimen.

Other limitations of the safety data in the pivotal study include the absence of data in patients with significant hepatic impairment as patients with ALT and/or AST > 3 x upper limit of the normal range (ULN) were excluded, as were patients with total bilirubin > 1.5 x ULN, and in patients with severe renal impairment (creatinine clearance < 30 mL/min). In addition, in the pivotal study there were limited data in patients identified as Black, Asian or Other as the majority of the patients in the safety population were identified as White (85%).

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of treatment with ixazomib in combination with Len/Dex in patients with RRMM treated with at least one prior therapy have been satisfactorily established in one pivotal Phase III Study C16010. The data summarised below relate to the first interim analysis of the pivotal study, which is the final analysis of PFS for statistical testing purposes.

- The median duration of follow-up was 14.8 months in the ixazomib regimen and 14.6 months in the placebo regimen. PFS based on independent review committee (IRC) assessment (primary efficacy endpoint) in the ixazomib regimen (n = 360) was 5.9 months longer than in the placebo regimen (n = 362), with median PFS being 20.6 months and 14.7 months respectively. The hazard ratio (HR) in the ITT

population was 0.742 (95% CI: 0.587, 0.939), p = 0.012, which translates into a 35% improvement in median PFS in the ixazomib regimen compared to the placebo regimen. In the ixazomib regimen, 129 (36%) patients experienced a PFS event (114 [32%] progressive disease (PD); 15 [4%] deaths) compared to 157 (43%) patients in the placebo regimen (145 [40%] PD; 12 [3%] deaths). The PFS events indicate that the primary benefit of treatment with the ixazomib regimen relative to the placebo regimen is a reduced risk of experiencing disease progression.

- The Kaplan-Meier (K-M) plot of PFS based on IRC assessment showed clear separation of the two treatment regimen curves in favour of the ixazomib regimen compared to the placebo regimen beginning at 8 months after initiation of treatment, and increasing over time.
- The HRs for PFS based on IRC assessment were consistently < 1 (that is, favouring the ixazomib regimen relative to the placebo regimen) across the pre-planned subgroups defined by age, sex, race, region, cytogenetic risk, ISS stage at screening, Eastern Cooperative Oncology Group (ECOG) performance status, number of prior therapies, types of prior therapies, and renal function. These results indicate a lower risk of progression or death in the ixazomib regimen compared to the placebo regimen in each of the subgroups.
- Overall survival (OS) in the ITT population was a key secondary efficacy endpoint. The median duration of follow-up was 14.8 months in the ixazomib regimen and 14.6 months in the placebo regimen. A total of 107 deaths were reported, representing 22% (107/486) of the pre-specified number of deaths projected for the final OS analysis in the ITT population. Median OS had not been reached in either of the two treatment regimens. However, the HR was 0.90 (95% CI: 0.615, 1.316), p = 0.586, indicating a non-statistically significant reduction of 10% in the risk of death in the ixazomib regimen relative to the placebo regimen. Of the 107 deaths included in the analysis, 51 (14%) had occurred in the ixazomib regimen and 56 (15%) had occurred in the placebo regimen.
- OS in high risk patients harbouring the del(17) chromosomal abnormality was a key secondary efficacy endpoint. The median duration of follow-up was 12.5 months in the ixazomib regimen and 14.6 months in the placebo regimen. A total of 13 deaths had occurred in these high risk patients, comprising 4 (11%) deaths in 36 patients in the ixazomib regimen and 9 (27%) deaths in 33 patients in the placebo regimen. The HR in the high risk harbouring del(17) population was 0.506 (95% CI: 0.144, 1.777) Median OS had not been reached in either of the two treatment regimens.
- In patients with progressive disease (114 [32%] in the ixazomib regimen; 145 [40%] in the placebo regimen), the median time to progression in the ITT population was 21.4 months (95% CI: 18.43, NE) in the ixazomib regimen and 15.7 months (95% CI: 13.21, 18.27) in the placebo regimen. The results indicate that ixazomib regimen delays time to progression by 5.7 months compared to the placebo regimen (HR = 0.712 [95% CI: 0.556, 0.912], p = 0.007).
- The confirmed overall response rate (ORR) (CR + PR [including sCR[12] and VGPR]) based on IRC assessment in the ITT population was 78.3% (n = 282) in the ixazomib regimen and 71.5% (n = 259) in the placebo regimen (odds ratio = 1.44 [95% CI: 1.03, 2.03]; p = 0.035). The confirmed CR rate in the ixazomib regimen was almost double that in the placebo regimen (11.7% [n = 42] versus 6.6% [n =

[12] sCR = stringent complete response

24], respectively; odds ratio = 1.87 [95% CI: 1.10, 3.16]; p = 0.019). The ORR in the ixazomib regimen relative to the placebo regimen remained relatively constant over time based on the treatment cycle, but the patient numbers were small after Cycle 18.

- Time to response was measured from date of randomisation to the first documentation of PR or better. In the response evaluable population (all responders), a response was achieved by 279 patients in the ixazomib regimen and 255 patients in the placebo regimen. The median time to response was rapid in both treatment regimens, being 1.0 month in the ixazomib regimen and 1.1 months in the placebo regimen (HR = 1.209 [95% CI: 1.014, 1.443]).
- The duration of response (DOR) was measured as the time from the date of first documentation of PR or better to the date of first documented PD. In the response evaluable population (all responders), events had occurred in 92 (33%) patients in the ixazomib regimen and 104 (41%) patients in the placebo regimen. The median DOR was 20.5 months (95% CI: 16.62, NE) in the ixazomib regimen and 15.0 months (95% CI: 11.99, NE) in the placebo regimen.
- Quality of life assessments demonstrated that treatment with the ixazomib regimen was not associated with deterioration in the quality of life over the assessment period, with quality of life in both the ixazomib and placebo regimens remaining largely unchanged at the end of the first analysis.

First round assessment of risks

- In the pivotal Study C16010, TEAEs were reported in 98% (351/360) of patients in the ixazomib regimen and 99% (355/360) of patients in the placebo regimen. In the overall safety analysis population 96% (951/990) of patients experienced at least one TEAE. The data indicate that nearly all patients treated with the proposed ixazomib regimen are at risk of experiencing at least one TEAE. The majority of TEAEs in both the pivotal study and the overall safety analysis population were reported by investigators to be related to the administered drug regimen. Drug regimen related TEAEs were experienced by 91% and 88% of patients the ixazomib and placebo regimens, respectively, in the pivotal study and 85% of patients in the overall safety analysis population. In the evaluation of risks discussed below, TEAEs refer to events reported regardless of causality unless otherwise stated.
- The data from the pivotal study suggest that most TEAEs can be managed by dose reductions (with or without symptomatic treatment) rather than discontinuation from treatment. In the pivotal study, TEAEs resulting in dose reduction of 1 or more of the 3 agents in the study regimen were reported in 52% of patients in the ixazomib regimen and 44% of patients in the placebo regimen, while TEAEs resulting in discontinuation of 1 or more of the 3 agents in the study regimen were reported in 19% and 17% of patients, respectively. In the pivotal study, TEAEs resulting in discontinuation from the full study drug regimen were reported in 13% of patients in the ixazomib regimen and 11% of patients in the placebo regimen, with the corresponding figure for ixazomib treated patients in the overall safety analysis population being 12%. As of the data cut-off date for the submission, 199 patients (55%) in the ixazomib regimen and 188 patients (52%) in the placebo regimen in the pivotal study were still on study treatment.
- TEAEs leading to discontinuation of 1 or more of the 3 agents in the study drug regimen in the pivotal study were reported in 19% of patients in the ixazomib regimen and 17% of patients in the placebo regimen. There were no TEAEs (PTs) leading to discontinuation of 1 or more of the 3 agents in the study drug regimen

with an incidence > 1% in either regimen. TEAEs leading to discontinuation in 3 or more patients in either the ixazomib or placebo regimens (respectively) were diarrhoea (5 [1%] versus 3 [< 1%]), fatigue (5 [1%] versus 3 [< 1%]), insomnia (≤ 1% in each regimen), cardiac failure (1 [< 1%] versus 4 [1%]), neutropenia (3 [< 1%] each regimen), peripheral sensory neuropathy (3 [< 1%] versus 2 [< 1%]), acute renal failure (≤ 1% in each regimen), thrombocytopenia (3 [< 1%] in each regimen), and platelet count decreased (≤ 1% in each regimen).

- The E-R analyses demonstrated a significant relationship ($p < 0.05$) between ixazomib exposure and TEAEs of rash, peripheral neuropathy, diarrhoea, nausea, vomiting, fatigue, thrombocytopenia, and anaemia. These TEAEs appear to be manageable by dose reduction and/or symptomatic treatment.

Risks associated with TEAEs of clinical importance

- The TEAEs of clinical importance nominated by the sponsor were heart failure, arrhythmias, myocardial infarction, rash, nausea, vomiting, diarrhoea, thrombocytopenia, neutropenia, liver impairment, peripheral neuropathy, encephalopathy, renal impairment, and hypotension. In the pivotal study, TEAEs of clinical importance reported in ≥ 5% more patients in the ixazomib regimen compared to the placebo regimen were diarrhoea (PT: 42% versus 36%), rash (pooled PTs: 35% versus 21%), thrombocytopenia (pooled PTs: 28% versus 14%), peripheral neuropathy (pooled PTs: 28% versus 21%), nausea (PT: 26% versus 21%), and vomiting (PT: 22% versus 11%). There was < 5% difference between the two treatment regimens in the incidence of patients experiencing all other TEAEs of clinical importance, namely, heart failure (pooled PTs), arrhythmias (pooled PTs), myocardial infarction (pooled PTs), neutropenia (pooled PTs), liver impairment (pooled PTs), encephalopathy (pooled PTs), renal impairment (pooled PTs), and hypotension (pooled PTs). The risks associated with the TEAEs of clinical importance reported in ≥ 5% more patients in the ixazomib regimen than in the placebo group in the pivotal study are reviewed below.
- The risk of experiencing thrombocytopenia (pooled PTs) was 2 fold greater in patients treated with the ixazomib regimen than with the placebo regimen, with the incidence being 28% and 14%, respectively. Furthermore, the risks of experiencing Grade 3 thrombocytopenia (pooled PTs) was greater in the ixazomib regimen than in the placebo regimen (10% versus 4%), as was the risk of experiencing a Grade 4 event (7% versus 3%). However, there were no deaths reported due to thrombocytopenia (pooled PTs) in either treatment regimen. Discontinuation of at least 1 of the 3 agents in the study drug regimen due to thrombocytopenia (pooled PTs) was reported infrequently in both treatment regimens, with < 1% of the patients in the ixazomib regimen and 2% of patients in the placebo regimen discontinuing treatment due to these events. Ixazomib and placebo doses were each held in < 1% of patients due to thrombocytopenia (pooled PTs), while 5% and 1% of patients had their dose reduced due to these events. The need for platelet transfusion was similar in the ixazomib and placebo regimens (6% and 5%, respectively). A similar percentage of patients in the ixazomib and placebo regimens had a haemorrhagic event of any grade (18% and 16%, respectively) or a Grade 3 or higher haemorrhagic event (2% and < 1, respectively). In both treatment regimens, median platelet counts generally demonstrated a cyclical pattern when measured throughout Cycles 1 through 3, with nadirs around Day 14 of each 28 day cycle and returning to baseline levels before the next cycle. The incidence of thrombocytopenia was highest in the first 3 months of treatment and then declined over time.
- The risk of diarrhoea was higher in the ixazomib regimen than in the placebo regimen (42% versus 36%), with Grade 3 diarrhoea, being reported in 6% and 2%

of patients in the two regimens respectively, and SAEs of diarrhoea being reported in 2% of patients in each regimen. No Grade 4 or 5 diarrhoea was reported in either of the two treatment regimens. The risk of discontinuation due to diarrhoea was low in both the ixazomib and placebo regimens (1% versus < 1%, respectively). The use of anti-propulsives to treat diarrhoea was reported in 18% of patients in the ixazomib regimen and 14% of patients in the placebo regimen. Dose reductions due to diarrhoea were reported for ixazomib in 3% of patients and for placebo in < 1%) patients, while lenalidomide dose was reduced in 3% and 2% of patients in the ixazomib and placebo regimens, respectively, and dexamethasone dose was reduced in 3% and 1% of patients in the ixazomib and placebo regimens, respectively. The incidence of diarrhoea was highest in the first 3 months of treatment in both treatment regimens and decreased over time.

- The risk of nausea was 5% higher in the ixazomib regimen (26%) than in the placebo regimen (21%), while the risk of vomiting was 2 fold higher in the ixazomib regimen than in the placebo regimen (22% versus 11%, respectively). Grade 3 or higher nausea was infrequent and only occurred in patients in the ixazomib regimen (2%). Grade 3 or higher vomiting was also infrequent and occurred in a similar proportion of patients in the ixazomib and placebo regimens (1% and < 1%, respectively). SAEs due to nausea and vomiting were each reported in < 1% of patients in the ixazomib regimen and no patients in the placebo regimen. In total, 3 patients, all in the ixazomib regimen, were hospitalised for management of nausea and/or vomiting. No patients in either of the two treatment regimens discontinued due to nausea or vomiting, while dose reductions due to nausea were reported in 2% of patients in the ixazomib regimen and 1% of patients in the placebo regimen and dose reductions due to vomiting were reported in 1% of patients in the ixazomib regimen and no patients in the placebo group. Standard anti-emetic agents were recommended (Per Protocol) for emesis if it occurred once treatment was initiated, and prophylactic anti-emetics were to be used at the physician's discretion. Prophylactic use of anti-emetics starting prior to the first dose of study drugs was reported in 5% of patients in the ixazomib regimen and 2% of patients in the placebo regimen, while 10% and 4% of patients, respectively, reported starting these agents for prophylactic use only after the first dose of study treatment. Nausea and vomiting both occurred most frequently in the first 3 months of treatment in both treatment regimens.
- The risk of rash (pooled PTs) was greater in the ixazomib regimen than in the placebo regimen (35% versus 31%, respectively), and the difference was primarily due to a higher frequency of low grade events (that is, Grades 1 and 2). Grade 3 rash (pooled PTs) was reported in 4% of patients in the ixazomib regimen and 1% of patients in the placebo regimen, while no patients in either of the two treatment regimens reported Grade 4 TEAEs, Grade 5 TEAEs or SAEs associated with rash. Rash (pooled PTs) leading to discontinuation of at least 1 of the 3 agents in the study drug regimen occurred in 1% of patients in the ixazomib regimen and < 1% of patients in the placebo regimen. The most common causes of rash reported in ≥ 5% of patients in either of the two treatment regimens were pruritus (10% ixazomib regimen versus 7% placebo regimen), maculopapular rash (9% ixazomib regimen versus 3% placebo regimen), and macular rash (6% in both regimens). No patient in either regimen in the pivotal study experienced in the pivotal study experienced Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). However, 2 (0.2%) patients in the overall safety analysis population were reported to have experienced SJS. In the pivotal study, the use of systemic anti-histamines was reported more frequently in the ixazomib regimen than in the placebo regimen (27% versus 19%, respectively).

- Updated safety data relating to the occurrence of rash in the ixazomib clinical program were submitted by the sponsor. The data identified a total of 9 patients with severe cutaneous adverse reactions (standardised MedDRA query (SMQ), narrow) as of the data lock point of 9 June 2015, including 7 patients treated with ixazomib (0.31% [7/2242] and 2 patients treated with placebo (0.31% [2/646]). The 7 cases in ixazomib treated patients included, 2 cases of erythema multiforme (both single agent), 2 cases of SJS (both in combination with Len/Dex), 1 case of cutaneous vasculitis (combination with Len/Dex), 1 case of TEN (combination with Len/Dex), and 1 case of DRESS syndrome (combination with Len/Dex). The 2 cases in placebo treated patients included 1 case of DRESS syndrome (combination with Len/Dex) and 1 case of SJS (combination with Len/Dex). Of the 7 cases reported with ixazomib, 5 patients experienced onset of rash after 1 to 8 weeks of treatment, 4 patients were over 70 years of age, and all were confounded with one or more medications that are associated with skin reactions.
- The risk of peripheral neuropathy (pooled PTs) was greater in the ixazomib regimen than in the placebo regimen (28% versus 21%, respectively), with both regimens having a 2% incidence of Grade 3 events and no patients in either regimen had a Grade 4 event. The majority of PT events in both treatment regimens were peripheral sensory neuropathy (19% ixazomib regimen versus 14% placebo regimen), with most of the remaining PT events being peripheral neuropathy (10% in the ixazomib regimen and 8% in the placebo regimen). Discontinuations due to peripheral neuropathy (pooled PTs) were infrequent (1% in each regimen).
- The risk of other TEAEs (pooled PTs) of clinical importance in the ixazomib regimen and placebo regimen (respectively) were heart failure (4% versus 3%), arrhythmia (13% each regimen; no increased risk of QT prolongation), myocardial infarction (1% versus 2%), neutropenia (30% versus 27%), liver impairment (6% versus 5%), encephalopathy (< 1% both regimens), renal impairment (8% versus 10%), and hypotension (6% each regimen).

Risks associated with TEAEs of special interest

- Skeletal related events were defined as new fractures (excluding vertebral compression or rib fractures), bone irradiation or surgery, or spinal cord compression. In the pivotal study, the incidence of skeletal related TEAEs was similar in the ixazomib and placebo regimens (4% versus 2%, respectively). The use of drugs affecting bone structure and mineralisation (for example, pamidronic acid or zoledronic acid), was similar in the ixazomib and placebo regimens (49% versus 48%, respectively).
- The prophylactic use of anti-thrombotic agents was recommended in all patients, due to the risk of thromboembolic events associated with the use of lenalidomide, and approximately 97% of patients in the pivotal study reported taking such agents. Thrombosis (SMQ) was reported in 7% of patients in the ixazomib regimen and 10% of patients in the placebo regimen, indicating that patients treated with the proposed ixazomib regimen are not at increased risk of thrombosis compared to patients treated with Len/Dex.
- In the pivotal study, TEAEs of herpes zoster were experienced by 4% of patients in the ixazomib regimen and 2% of patients in the placebo regimen. The use of antiviral agents was at the discretion of the treating physician and 67% of patients in the ixazomib regimen and 66% of patients in the placebo regimen reported taking antiviral agents during the study. In the pivotal study, herpes zoster infection rarely occurred in patients taking antiviral agents prophylactically (1 patient in each regimen).

- New primary malignancies were reported in 2% of patients in the ixazomib regimen and 1% of patients in the placebo regimen during treatment, and < 1% (n = 1) of patients in each regimen during follow-up. Of the 13 new primary malignancies during treatment, 4 were non-haematologic (excluding skin malignancies) and 2 were haematologic. In the ixazomib regimen the reported malignancies were 1 case of myelodysplastic syndrome, 5 cases of solid tumours, and 3 cases of skin cancers. Four of the 5 patients with a newly diagnosed solid tumour had a clinically relevant medical history. In the placebo regimen the reported malignancies were 1 case of myelodysplastic syndrome, 1 case of solid tumour and 4 cases of skin cancers.

Risks associated with TEAEs (PTs)

- In the pivotal study, TEAEs (PTs) were reported in ≥ 20% of patients in either the ixazomib regimen or the placebo regimen (respectively) were, diarrhoea (42% versus 36%,), constipation (34% versus 25%), fatigue (28% versus 26%), anaemia (26% versus 25%), neutropenia (26% versus 22%), nausea (26% versus 21%), peripheral oedema (25% versus 18%), vomiting (22% versus 11%), back pain (21% versus 16%), nasopharyngitis (20% versus 18%), thrombocytopenia (20% versus 10%), and insomnia (19% versus 25%).
- TEAEs (PT) reported in ≥ 5% more patients in the ixazomib regimen than in the placebo regimen in the pivotal study were diarrhoea (42% versus 36%), constipation (34% versus 25%), nausea (26% versus 21%), peripheral oedema (25% versus 18%), vomiting (22% versus 11%), back pain (21% versus 16%), thrombocytopenia (20% versus 10%), upper respiratory tract infection (19% versus 14%), peripheral sensory neuropathy (19% versus 14%), and maculopapular rash (9% versus 3%). TEAEs (PT) reported in ≥ 5% fewer patients in the ixazomib regimen than in the placebo regimen were insomnia (19% v 25%), muscle spasm (18% versus 25%), and pyrexia (13% versus 19%).
- For all TEAEs, except thrombocytopenia (PT), reported in ≥ 5% more patients in the ixazomib regimen than in the placebo regimen in the pivotal study the difference between the two treatment regimens was primarily due to a higher frequency of Grade 1 and 2 events. For thrombocytopenia, the difference in frequency of TEAEs was across all grades, including Grade 3 or higher. However, potential clinical consequences of thrombocytopenia were similar in the ixazomib and placebo regimens, with bleeding (all grades) being reported in 18% and 16% of patients, respectively, and the need for platelet transfusions being reported in 6% and 5% of patients, respectively.
- In the pivotal study, the risk of experiencing a Grade 3 TEAE (PT) was higher in the ixazomib regimen than in the placebo regimens (49% versus 43%, respectively). Grade 3 TEAEs (PT) reported by ≥ 5% of patients in either the ixazomib or placebo regimen (respectively) were neutropenia (15% versus 12%), anaemia (9% versus 13%), thrombocytopenia (8% versus 3%), diarrhoea (6% versus 2%), and pneumonia (6% versus 7%). The only Grade 3 TEAE (PT) reported in ≥ 5% more patients in the ixazomib regimen than in the placebo regimen was thrombocytopenia (8% versus 3%).
- In the pivotal study, the risk of experiencing a Grade 4 TEAE (PT) was similar in the ixazomib and placebo regimens (15% versus 14%, respectively). Grade 4 TEAEs (PT) reported by ≥ 1% of patients in either the ixazomib or placebo regimens (respectively) were thrombocytopenia (6% versus 2%), neutropenia (4% each), hypokalaemia (2% versus < 1%,), platelet count decreased (1% each), sepsis (1% versus < 1%), neutrophil count decreased (< 1% versus 1%), pneumonia (< 1% versus 1%), and septic shock (< 1% versus 1%). The only Grade 4 TEAE (PT)

reported in ≥ 2% more patients in the ixazomib regimen than in the placebo regimen was thrombocytopenia (6% versus 2%).

- There was no evidence from the pivotal study that the addition of ixazomib to Len/Dex increases the risk of death. In the pivotal study, the incidence of on-study deaths, defined as occurring within 30 days of the last dose of study drug, was similar in the ixazomib and placebo regimens (3% and 5%, respectively). Of the 29 on-study deaths (12 ixazomib regimen, 17 placebo regimen), 5 were reported as being related to study drug treatment (3 in the ixazomib regimen [pulmonary embolism, fungal pneumonia, coma with concurrent stroke] and 2 in the placebo regimen [myocardial infarction, pulmonary embolism]). One additional patient in the ixazomib regimen died 31 days after the last dose of study drug due to Grade 4 influenza and Grade 5 staphylococcal bacteraemia. The investigator considered these two events to be related to the full drug regimen and noted immunosuppression due to myeloma to be an alternative aetiology. Of the 29 on-study deaths reported in the pivotal study, 8 (28%) were attributed to disease progression (6 patients in the ixazomib regimen and 2 patients in the placebo regimen).
- In the overall safety analysis population, there were 41 (4%) on-study deaths. The most common causes of death were plasma cell myeloma (6 patients; < 1%), cardiac arrest (2 patients; < 1%), cardiorespiratory arrest (2 patients; < 1%), endometrial cancer (2 patients; < 1%), hepatic failure (2 patients; < 1%), pulmonary embolism (2 patients; < 1%), and septic shock (2 patients; < 1%). Of the 41 deaths, 5 were considered related to the study drug regimen (1 x respiratory syncytial viral pneumonia; 1 x cardiorespiratory arrest; 1 x coma with concurrent stroke; 1 x pulmonary embolism; and 1 x fungal pneumonia). Of the 41 on-study deaths, 18 (44%) were attributed to disease progression. There were 30 (3%) deaths within 90 days of the first dose of study drug. The most common causes of death during this time were plasma cell myeloma (6 patients; < 1%), cardiac arrest (2 patients; < 1%), endometrial cancer (2 patients; < 1%), and hepatic failure (2 patients; < 1%).

Risks associated with special groups (pivotal study)

- The risk of treatment with both treatment regimens increased with age. There were limited safety data on the risks of treatment in patients aged > 85 years. However, no adjustment to the starting dose of ixazomib appears to be required based on age. The risks of some TEAEs were greater in females than in males (that is, diarrhoea, nausea, vomiting), and there was a higher percentage of female than male patients reporting TEAEs resulting in dose reduction of 1 or more of the 3 agents in the ixazomib regimen (63% versus 44%) and TEAEs resulting in dose modification of 1 or more of the 3 agents in the ixazomib regime (77% versus 66%). However, no adjustment to the starting dose of ixazomib appears to be required based on sex.
- There were no safety data in the pivotal study in patients with significant hepatic impairment. However, based on the PK study in patients with advanced solid tumours with hepatic impairment (Study C16018) a starting ixazomib dose of 3 mg is recommended for patients with moderate to severe hepatic impairment and a starting ixazomib dose of 4 mg is recommended for patients with mild hepatic impairment (that is, no adjustment to the starting dose).
- Based on the PK study in patients with renal impairment and normal renal function or severe renal impairment (CrCl < 30 mL/min, including ESRD) a starting ixazomib dose of 3 mg is recommended for patients with severe renal impairment, including ESRD renal disease requiring dialysis. There were no PK data in patients

with mild or moderate renal impairment. However, safety data from the overall safety analysis population based on baseline creatinine clearance suggests that the risk of a number of TEAEs is higher in patients with baseline CrCl ≥ 30 to < 60 mL/min compared to patients with baseline CrCl ≥ 60 mL. The results suggest that the starting dose of ixazomib should also be reduced to 3 mg in patients with moderate renal impairment (CrCL ≥ 30 to < 60 mL/min).

First round assessment of benefit-risk balance

The benefit-risk balance of the proposed ixazomib regimen is favourable for the treatment of patients with RRMM whose disease has progressed on at least one prior therapy.

First Round Recommendation Regarding Authorisation

It is recommended that ixazomib in combination with lenalidomide and dexamethasone be approved for the treatment of patients with relapsed and/or refractory multiple myeloma whose disease has progressed on at least one prior therapy.

Clinical Questions, and Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical questions, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

It is considered that the benefit-risk balance is favourable for the proposed ixazomib regimen for the treatment of patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy. This assessment is based on the totality of the submitted efficacy and safety data.

Second round recommendation regarding authorisation

It is recommended that the proposed treatment regimen of ixazomib in combination with lenalidomide and dexamethasone be approved for the treatment of patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP version 1.0 dated 30 June 2015 (data lock point 30 October 2014) with the Australian Specific Annex version 1.0 dated October 2015 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Ongoing safety concerns

Summary of safety concerns	
Important identified risks	· Thrombocytopenia · Gastrointestinal events (specifically nausea, vomiting, diarrhoea
Important potential risks	· Severe dermal events · Peripheral neuropathy
Missing information	· Use in pregnancy/lactation · Long term safety

Pharmacovigilance plan

Table 8 summarises the pharmacovigilance activities. The content of the table is based on the information provided in the EU-RMP and the ASA: Risk minimisation activities.

Table 8: Proposed Pharmacovigilance activities

Proposed Pharmacovigilance activities	
Important identified risks	
Thrombocytopenia	· Routine pharmacovigilance, including event specific follow-up form
Gastrointestinal events (specifically nausea, vomiting, diarrhoea)	· Routine pharmacovigilance
Important potential risks	
Severe dermal events	· Routine pharmacovigilance, including event specific follow-up form
Peripheral neuropathy	· Routine pharmacovigilance
Missing information	
Use in pregnancy/lactation	· Routine pharmacovigilance
Long-term safety	· Routine pharmacovigilance; · Additional pharmacovigilance: study C16010, C16014, C16019, and C16021

Risk minimisation plan

The sponsor proposes routine risk minimisation for all safety concerns[13]. No additional risk minimisation has been proposed in the EU-RMP. The sponsor also states in the ASA:

> The risk minimisation activities proposed for Australia are identical to the risk minimisation activities proposed in the EU. The text proposed for the Australian PI is consistent with the proposed text of the EU Summary of Product Characteristics (SmPC).

Reconciliation of issues outlined in the RMP report

Table 9 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

[13] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging

Table 9: Reconciliation of issues in the first round RMP evaluation report

Reconciliation of issues in the round 1 RMP evaluation report
TGA recommendation 1: Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
Sponsor's response: The sponsor has reviewed the clinical and nonclinical evaluation reports and the questions raised by the clinical evaluator. The sponsor confirms that there are no additional safety considerations that need to be addressed in the RMP.
RMP evaluator comment: The sponsor's response is noted. Please refer to the recommendations made in the nonclinical evaluator report.
TGA recommendation 2: On 20 November 2015, the US FDA granted approval for ixazomib in combination with lenalidomide and dexamethasone to treat people with multiple myeloma who have received at least one prior therapy. No REMS was required.[14] The evaluator would like to draw the Delegate's attention to the approved indication in the US and the difference between this and the proposed indication in Australia: 'Ninlaro is a proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.'
Sponsor's response: The originally proposed indication in Australia was generally consistent with the approved indication in the United States. Please note that the wording of the proposed indication in Australia has been modified based on the clinical evaluator's comments on the PI. Please refer to the clinical response document and the Ninlaro annotated PI.
RMP evaluator comment: The sponsor's response is noted.
TGA recommendation 3: The sponsor should provide an update to the market authorisation status overseas. Explanation should be provided for any decision of deferral, rejection, or withdrawal of an application.
Sponsor's response: The updated overseas regulatory status is provided
RMP evaluator comment: The sponsor has advised that all its overseas applications are still ongoing except in the USA where the product was approved in 2015. The evaluator has noted that on 26 May 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the

[14] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Reconciliation of issues in the round 1 RMP evaluation report
marketing authorisation for ixazomib (Ninlaro), intended for the treatment of multiple myeloma due to insufficient benefits demonstrated in the clinical trial[15]. It is noted that this was announced around the time that the sponsor's response was submitted to TGA, and that the sponsor has requested a re-examination of the CHMP opinion. The evaluator wishes to draw the Delegate's attention to this recent overseas regulatory action.
TGA recommendation 4: The following adverse events have been identified in clinical trials and should be added to the ASA as important potential risks: a. Peripheral oedema b. Hepatotoxicity
Sponsor's response: a. the sponsor does not consider peripheral oedema as an important potential risk for inclusion in the ASA. b. The sponsor does not consider liver impairment (hepatotoxicity) as an important potential risk for inclusion in the ASA.
RMP evaluator comment: the sponsor has provided justification to its position based on the results of the 23 months follow-up analyses. Therefore, it is acceptable that these risks are not listed as important potential risks at this stage. The sponsor should monitor the incidence and severity of these adverse events continuously and report findings in the Periodic Safety Update Reports (PSURs).
TGA recommendation 5: The following safety concerns have been associated with the use of bortezomib that are missing from the summary of safety concerns for ixazomib. The sponsor should provide justification to why they are unrelated to ixazomib or add them to the ASA as important potential risks: a. Neutropenia and neutropenia with infection b. Cardiac toxicity c. Pulmonary toxicity d. Tumour lysis syndrome e. Posterior reversible encephalopathy syndrome
Sponsor's response: Although bortezomib and ixazomib are both proteasome inhibitors, these 2 agents are distinct molecular entities with their own unique safety profiles. The sponsor's assessment of safety concerns for ixazomib is based on the available nonclinical and clinical data for this molecule. With the exception of posterior reversible encephalopathy syndrome (PRES), the sponsor does not consider the following as either safety concerns or important potential risks associated with ixazomib use based on the currently available data: neutropenia, neutropenia with infection, cardiac toxicity, pulmonary toxicity, and tumour lysis syndrome.

[15] EMA Refusal of the marketing authorisation for Ninlaro (24 June 2016 update)

Reconciliation of issues in the round 1 RMP evaluation report
RMP evaluator comment: Posterior reversible encephalopathy syndrome has been added as an important potential risk. The sponsor has provided justification to its position through clinical trial results, including comparison between the ixazomib group and the placebo group, and follow-up analysis. The sponsor's justifications are acceptable. However, the sponsor should continue to monitor and report these adverse events in the PSURs.
TGA recommendation 6: The sponsor should provide analysis on the applicability of the findings from Study C16021 in Australia. If the sponsor considers that it is not applicable, alternative plans should be made and submitted to the TGA for evaluation.
Sponsor's response: Four ongoing Phase III clinical studies were proposed as additional pharmacovigilance (PhV) activities in Section 2.4 of the PhV plan of the ASA to the ixazomib EU RMP version 1.0 (30 June 2015). Two of these studies, including the ongoing C16021 study, were removed from the PhV plan of the ixazomib EU RMP v1.1 (20 January 2016) at the request of the EMA upon their review of the RMP, as patients in these studies were considered to differ from the target population in the proposed indication. Consequently, Section 2.4 of the PhV plan of the ASA has been revised to remove these studies. The remaining 2 ongoing studies in the PhV plan, including the pivotal Phase III Studies C16010 and C16019, are expected to add valuable information on the long-term safety profile of ixazomib.
RMP evaluator comment: The sponsor's response is acceptable. Given that the two studies remain in the RMP are both ongoing Phase III trials that include Australian patients, the evaluator expects that they will not be affected by the decision made by the EMA on the current submission.
TGA recommendation 7: The sponsor should provide an update on safety findings from the ongoing studies included in the pharmacovigilance plan. They include Studies C16010, C16014, and C16019. Any significant findings should be accompanied with analysis.
Sponsor's response: The Phase III Study C16014 was removed from the PhV plan of the ixazomib EU RMP v1.1 (20 January 2016) at the request of the EMA upon their review of the RMP, as patient population in this study was considered to differ from the target population in the proposed indication. No new significant safety findings have been identified from the ongoing Study C16010 since the submission of this application; however, updated information is provided. Study C16019 is ongoing in a double blinded manner and no safety findings have been identified (detail was provided in the response).
RMP evaluator comment: The sponsor's response is acceptable.
TGA recommendation 8: The sponsor should provide justification to why it considers routine risk minimisation is sufficient to mitigate all the safety concerns.
Sponsor's response: Given the current safety profile of ixazomib, the sponsor believes that the proposed risk minimization activities (that is, labelling [PI and CMI]

Reconciliation of issues in the round 1 RMP evaluation report
and packaging) are appropriate. This proposal is consistent with other approved products in this drug class.
RMP evaluator comment: The sponsor has provided adequate justification for the use or routine risk minimisation alone, and this approach is considered acceptable.
TGA recommendation 9: Even though 10 cases of overdose may not be a large proportion in 20 clinical trials, medication error is a preventable risk that can lead to life threatening consequences during chemotherapy. One measure proposed by the sponsor to mitigate the risk is supervision by physicians experienced in the management of multiple myeloma. Doctors working in the clinical trials would be experienced in the management of multiple myeloma, which did not prevent the occurrence of 10 cases of overdose. The sponsor should provide justification to why it considers the two measures will effectively mitigate the risk in post-authorisation stage and why additional risk minimisation is not required.
Sponsor's response: The sponsor believes that the proposed commercial packaging configuration, clear instructions in each blister wallet (1 capsule each) and the provision of the CMI in each single pack, will promote patient compliance with the oral dosing regimen and assist in preventing inadvertent dosing errors.
RMP evaluator comment: The sponsor's response is acceptable.
TGA recommendation 10: As the evaluation in the EU and Australia progress, the sponsor should confirm that the risk minimisation measures, including product labels remain identical, or update the ASA to reflect the differences.
Sponsor's response: The sponsor accepts and confirms that any changes to the risk minimization measures, including products labels, will be appropriately reflected in the ASA.
RMP evaluator comment: Given the recent decision by the CHMP, this may no longer be applicable.
TGA recommendation 11: As the product is to be used in combination with lenalidomide, it is recommended that the Delegate considers adding pregnancy and women of childbearing potential as contraindications for Ninlaro lenalidomide combination therapy in the PI.
Sponsor's response: The sponsor proposes to include the following text in the Contraindication section of the Australian Package Insert: *As Ninlaro is administered in combination with lenalidomide and dexamethasone, refer to the Product Information for these products for respective contraindications.* *This approach provides prescribers with the guidance to refer to the approved labelling for the other products utilized in this combination drug regimen (ie, dexamethasone and lenalidomide) for a comprehensive, current view of all contraindications associated with these products.*

Reconciliation of issues in the round 1 RMP evaluation report
RMP evaluator comment: The sponsor's response is noted. The recommendation remains for the Delegate's consideration.
TGA recommendation 12: The US FDA approved product label contains the following advice on dose modification in the table 'Dose Modification Guidelines for Ninlaro in Combination with Lenadomide and Dexamethasone'. In comparison, dose modification advice on neutropenia is not explicitly listed in the draft Australian PI: · Withhold Ninlaro and lenalidomide until absolute neutrophil count is at least 500/mm^3. Consider adding granulocyte colony stimulating factor (G-CSF) as per clinical guidelines. · Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume Ninlaro at its most recent dose. · If absolute neutrophil count falls to less than 500/mm^3 again, withhold Ninlaro and lenalidomide until absolute neutrophil count is at least 500/mm^3. · Following recovery, resume Ninlaro at the next lower dose and resume lenalidomide at its most recent dose. · It is recommended to the Delegate that advice on neutropenia be added to improve patient safety.
Sponsor's response: The PI has been revised to include dose modification advice on neutropenia.
RMP evaluator comment: The sponsor has addressed the RMP Evaluators concern. The PI change is referred to the Delegate for their consideration.

Key changes to the updated RMP

In their response to the TGA requests for information the sponsor provided updated EU-RMP version 1.1 dated 20 January 2016 (data lock point 30 October 2014) with the Australian Specific Annex version 1.1 dated June 2016. Key changes from the version evaluated in the first round are summarised below in Table 10.

Table 10: Key changes to the revised RMP

Key changes to the revised RMP	
Safety specification	Important identified risks: Peripheral neuropathy has been upgraded from an important potential risk. Important potential risks: Herpes zoster infections, and posterior reversible encephalopathy syndrome have been added.
Pharmacovigilance activities	Routine pharmacovigilance has been proposed for the newly added safety concerns. Upon the EMA's request, the two studies C16014 and C16021 have been removed from the pharmacovigilance plan due to difference in patient population.
Risk minimisation activities	Routine risk minimisation has been proposed for the newly added safety concerns.

Summary of recommendations

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP version 1.1 dated 20 January 2016 (data lock point 30 October 2014) with the Australian Specific Annex version 1.1 dated June 2016 and any future updates as agreed with the TGA.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Treatment options for patients with relapsed or refractory multiple myeloma (RRMM) have been increased with the availability of thalidomide, lenalidomide, bortezomib and pomalidomide based regimens in addition to chemotherapy protocols. Regimens for the treatment of RRMM including thalidomide and its derivatives been incorporated into the most recent clinical practice guidelines of the Myeloma Foundation of Australia (2015), however, these guidelines precede the registration of bortezomib. For patients with RRMM, entry into clinical trials remains a primary management decision, given the ongoing poor outcome for these patients. The use of thalidomide or lenalidomide is limited by the occurrence of peripheral neuropathy and risk of thromboembolism.

Bortezomib, the first registered 20S proteasome inhibitor, is registered for use in patients with newly diagnosed MM eligible for stem cell transplant, in patients ineligible for high dose chemotherapy and for patients with relapsed or refractory disease. Prior to bortezomib registration, the most appropriate therapy for RRMM patients was the combination of lenalidomide and dexamethasone, which had been demonstrated to have increased efficacy over lenalidomide monotherapy.

Entry into clinical trials remains a consideration for patient management, despite the availability of recently increased therapeutic options, as relapse is inevitable after first-line therapy and the optimal order of therapies has not been established.

In regard to ixazomib, the sponsor states "a new generation proteasome inhibitor is required to improve clinical outcomes with greater efficacy, less toxicity, and greater patient convenience".

Table 11: The overseas regulatory status

Country	Dates	Indication
US FDA	Approval date 20 November 2015	Ninlaro is a proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
EMA (As per website on 29 August	CHMP meeting 23-26 May 2016	Negative decision: "The company presented results from one main study involving 722 adults with multiple myeloma whose

Country	Dates	Indication
2016)		disease had not responded to or had come back after previous treatment. The study compared Ninlaro with placebo (a dummy treatment), both taken together with the medicines lenalidomide and dexamethasone. The main measure of effectiveness was progression-free survival (how long the patients lived without their disease getting worse)." "The CHMP considered that the data from the main study were insufficient to demonstrate a benefit of Ninlaro in the treatment of multiple myeloma. The company had proposed restricting the use of the medicine to patients whose disease is more difficult to treat and had come back after one previous treatment, and to those whose disease had come back after at least two previous treatments. However, the data in these subgroups were not compelling enough and the rationale for assuming greater effectiveness in these patients was not clear." Takeda has requested a re-examination of the CHMP decision. The CHMP met on 5 September 2016 to reassess the submission.
Health Canada	4 August 2016	Approved indication: Ninlaro [ixazomib (as ixazomib citrate)] 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.

The difference in approval status of the FDA and EMA results from the difference in outcome based upon first and second interim analyses of the pivotal study assessed by the EMA, whereas the FDA requested further efficacy and safety analyses based upon a later cut-off.

Quality

The pharmaceutical data was evaluated to the satisfaction of the clinical chemistry evaluation section. There were no outstanding chemistry comments regarding the product information.

GMP clearance is confirmed.

The shelf-life of the product is 3 years when stored below 30°C.

Nonclinical

The summary of non-clinical data reported:

- The primary pharmacology studies lend some support for the proposed indication. The pharmacokinetic profile was comparable between human and multiple other species.
- In vitro and in vivo studies demonstrated CYP mediated metabolism. Ixazomib citrate is not expected to alter exposures to CYP450 substrates. Inhibitors of CYP450 enzymes are not expected to significantly alter the pharmacokinetics of ixazomib. As CYP3A4 and 1A2 have a minor role in the metabolism of ixazomib, inducers of these CYPs may increase the contribution of CYP450s to the clearance of ixazomib.

- In vitro, ixazomib was reported to be a low affinity substrate of P-gp, with P-gp mediated ixazomib transport accounting for 19% of the total transport of the drug in Caco-2 cells. In vitro, ixazomib was reported not to be a substrate for BCRP, MRP2 and OATPs, or an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Consequently, based on the in vitro data it can be reasonably inferred that ixazomib is unlikely to cause or be susceptible to clinically significant drug-drug interactions with substrates or inhibitors of drug transporters.
- The combined animal safety studies revealed the following findings of potential clinical relevance:
  - Gastrointestinal disturbances
  - Peripheral and central neuronal degeneration following repeated dose exposure in dogs
  - Reduced immunity as a result of lymphoid depletion
  - Bone marrow hypocellularity
  - Possible alterations in haematological parameters
  - No adverse effects were seen on cardiovascular function in dogs, nor respiratory function in rats.
- The safety of the combination of ixazomib citrate with lenalidomide and dexamethasone has not been assessed in submitted nonclinical studies.
- Provided adequate clinical safety data are available for the combination use, there are no objections on nonclinical grounds to the registration of ixazomib citrate for the proposed indication.
- The draft PI should be amended.

Clinical

Pharmacology

Fourteen clinical pharmacology studies were evaluated.

An interim and final population pharmacokinetic analysis was provided.

For details please see Attachment 2.

Absorption

Median T_{max} was 1 hour and t½ ranged 3.6 to 11.3 days.

Dose proportionality was observed for oral doses ranging 1.4 mg to 8.9 mg (that is the proposed dose is within this range).

A mass balance study demonstrated 62.1% parent drug absorption into the systemic circulation.

A formal bioavailability study was not performed; the evaluator and Delegate accept the sponsor's explanation for not performing this.

There was bioequivalence of the two dose formulations used during clinical development, including the final product.

A satisfactory explanation for not providing dose equivalence data between strengths was provided. Combinations of the 2.3mg and 3mg capsules cannot be used to deliver the proposed maximum dose of 4mg.

A significant effects on PK parameters following a high-fat meal were observed - decreased total systemic exposure $AUC_{(0\text{-}216h)}$ of ixazomib by 28%, and decreased C_{max} by 69%. The advice contained in the dosing and administration section of the PI recommends administration on an empty stomach or at least two hours after food, taken at the same time each day.

Repeat dose administration studies demonstrated an accumulation ratio of 2.09 to 2.12; terminal half-life was not accurately estimated.

Distribution

Population PK assessed Vd of ixazomib is 543 L. The drug is highly bound to albumin (unaffected by renal or hepatic impairment) and moderately bound to human alpha 1-acid glycoprotein.

Extensive partitioning into red blood cells, presumed binding to red cell proteasomes, was observed across studies, with AUC ratio plasma to red cells 1:10. No further tissue distribution data was provided.

Metabolism

Extensive metabolism (approximately 96.8%) was observed, with only 3.2% of unchanged drug excreted in urine.

The relative contribution of in vitro CYP enzymes to metabolism are: 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (< 1%). The schematic drug metabolic pathways are shown in the pre-clinical evaluation report.

No definitive data on metabolites in humans, or the effects of genetic polymorphisms were provided.

Excretion

A radiolabelled mass balance study of oral ixazomib (Study C16016) demonstrated renal clearance (CL) values on Days 1 and 15 were 0.07 L/hour and 0.06 L/hour, respectively. These values are approximately 3.5% of the total body CL estimate of 1.86 L/hour derived from the population PK analysis.

Ixazomib is excreted as metabolites in urine and faeces, with a ratio of approximately 3:1.

Pharmacokinetics in special populations

Hepatic impairment

Moderate and severe hepatic impairment increased systemic exposure by 32% and 23% respectively, and increased C_{max} by 27% and 21% respectively.

Dose adjustment for patients with moderate or severe hepatic impairment to 3 mg is recommended.

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. For patients with severe renal impairment (CrCl < 30 ml/min, or end stage renal disease requiring dialysis), the starting dose should be 3 mg.

Elderly

No dose adjustment is required based upon age alone.

Sex

No dose adjustment is required based upon patient sex.

Ethnicity

No dose adjustment is required based upon patient race.

Pharmacodynamics

Maximum 20S proteasome inhibition (E_{max}) was dose-dependent, and was approximately 80% after Single dose and multiple dose administration in patients who received the maximum tolerated dose (MTD). Prolonged inhibition of 20S proteasome activity was not apparent, consistent with reversible inhibition of the 20S proteasome.

Effect on QTc interval

There was no demonstrated effect on QTc interval, and no clinically meaningful differences were observed comparing patients receiving the placebo (Len/Dex) and active treatment arm ixazomib/(Len/Dex)) of the pivotal study.

Efficacy

One pivotal phase III study and two supportive Phase I studies were presented.

Pivotal study C16010

A Phase III, randomized, double blind, multicentre study comparing oral MLN9708 plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma.

Between 28 August 2012 and 27 May 2014, a total of 722 patients were randomised at 147 study centres in 26 countries. The majority of patients (67%, n = 483) were from Europe, with the remainder being from the Asia-Pacific region (20%, n = 143), and North America (13%, n = 96). The study included 17 (2%) patients from Australia.

The submitted clinical study report (CSR) was dated 27 May 2015. The data cut-off date for the results of the first interim analysis (final analysis of PFS for statistical testing purposes) reported in the CSR was 30 October 2014, and 387 patients were continuing on treatment at that date (199 in the ixazomib regimen [55%] and 188 [52%] in the placebo regimen).

Primary objective

Primary objective was to determine whether the addition of oral ixazomib to background therapy of lenalidomide and dexamethasone (Len/Dex) improves progression free survival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM) who have been treated with at least 1 line of prior therapy.

Secondary objectives

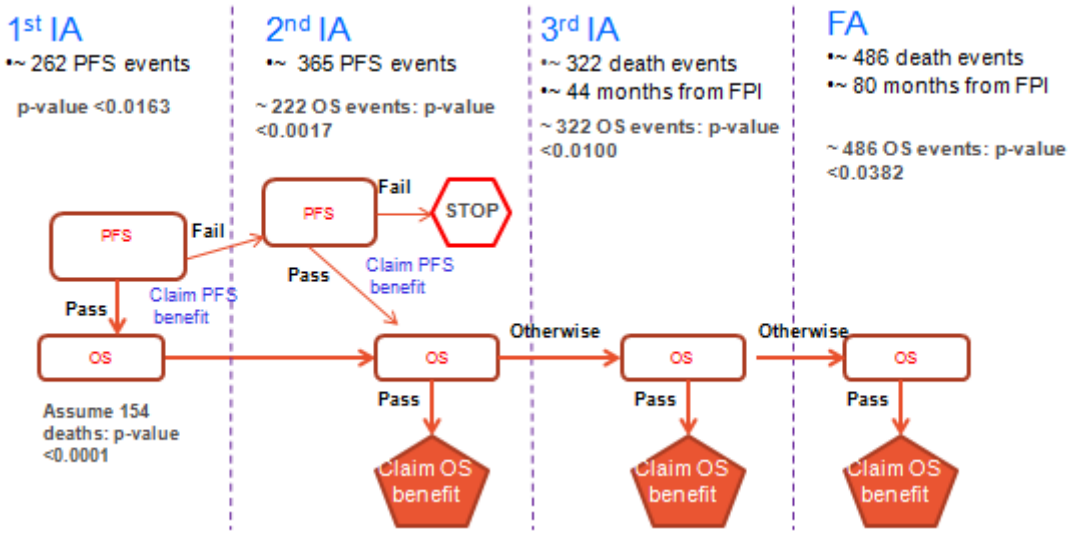
Secondary objectives were:

1. to determine whether the addition of oral ixazomib to Len/Dex improves overall survival (OS); and
2. to determine whether the addition of oral ixazomib to Len/Dex improves OS in high-risk patients carrying the genetic variation del(17).

Patients received 4 mg ixazomib or placebo as per the proposed schedule for registration on days 1, 8, and 15 plus 25 mg lenalidomide on Days 1 through 21 and 40 mg dexamethasone on Days 1, 8, 15, and 22 of a 28 day cycle.

The schedule for interim and final analysis is shown in the Figure 3 (IA =interim analysis, FA = final analysis):

Figure 3: Statistical assumptions in C16010



Treatment continued until disease progression (independently reviewed) based on the International Myeloma Working Group criteria, or unacceptable toxicity (as assessed by CTCAE v 4.03).

Inclusion required patients to have received 1 to 3 prior lines of therapy (full inclusion and exclusion criteria are shown in Table 29 in Attachment 2.

Major protocol deviations occurred in 4% of the study population, the most commonly occurring event being compliance ≤ 70%.

Baseline demographics and disease characteristics were well balanced and consistent with the wider population of patients with RRMM. Seventy percent of the whole study population had previously been exposed to bortezomib containing regimens; a similar proportion of each study arm was refractory to any prior immunomodulatory drugs (IMiD) (11% of the total study population). Sixty percent of the study population had undergone prior stem cell transplant.

Primary outcome

Primary outcome was progression-free survival.

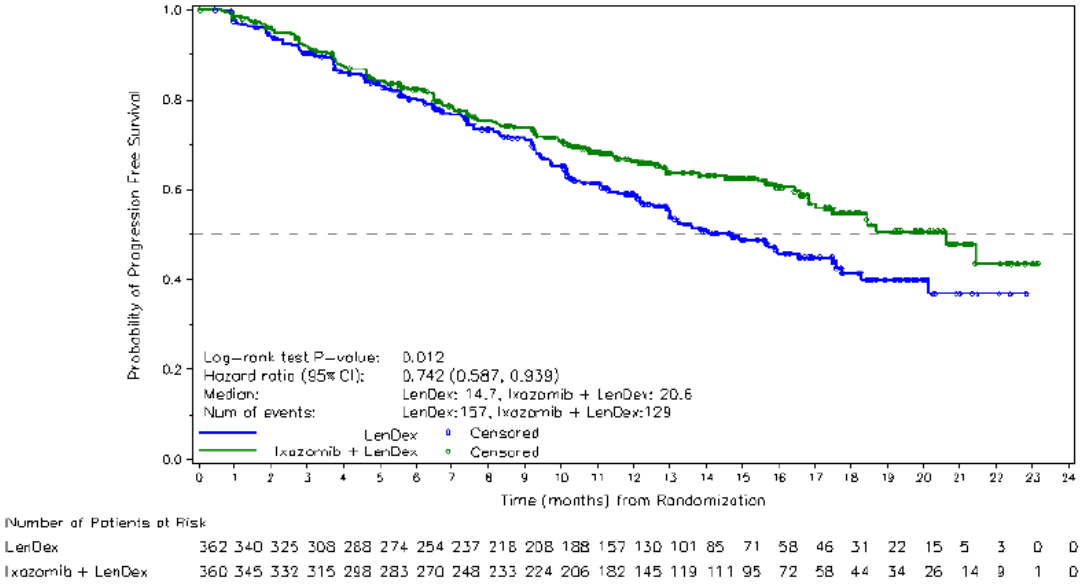
First pre-specified interim analysis (cut-off 30 October 2014)

This analysis was planned to be performed when approximately 262 of the IRC-assessed PFS events (disease progression or death) had occurred.

The sponsor states that "*once the primary endpoint, PFS as assessed by the [IRC] was met, that would be the final statistical testing of PFS. In other words, if the primary endpoint was met at the first analysis, per group sequential design, the focus of the next analysis would be OS. If the primary endpoint was not met at the first analysis, the second analysis was a second chance to test the study's hypothesis*". The study was designed to permit re-evaluation of PFS at two further analysis time-points if the first PFS analysis did not demonstrate a statistically significant result. Demonstration of a PFS benefit at first analysis, subsequent analyses would proceed to analyse overall survival.

At the first initial analysis, 286 PFS events had occurred, and there was a statistically significant reduction in the hazard of independently assessed PFS; PFS hazard ratio 0.74 (95% CI 0.59, 0.94), p = 0.012. The estimate of median duration of PFS was 20.6 months for the ixazomib + Len/Dex arm compared to 14.7 months for the Len/Dex arm.

Figure 4: C16010 - Kaplan-Meier plot of PFS survival based on IRC assessment; ITT population



Of note, at the time-point when median PFS is reached for the ixazomib arm, there are approximately 15 of the initial 362 patients still at risk.

According to the statistical analysis plan, this first analysis would be the first and final analysis for PFS for statistical testing purposes.

The study independent data monitoring committee reported that the stopping boundary had been crossed at this analysis.

Second pre-specified interim analysis of PFS

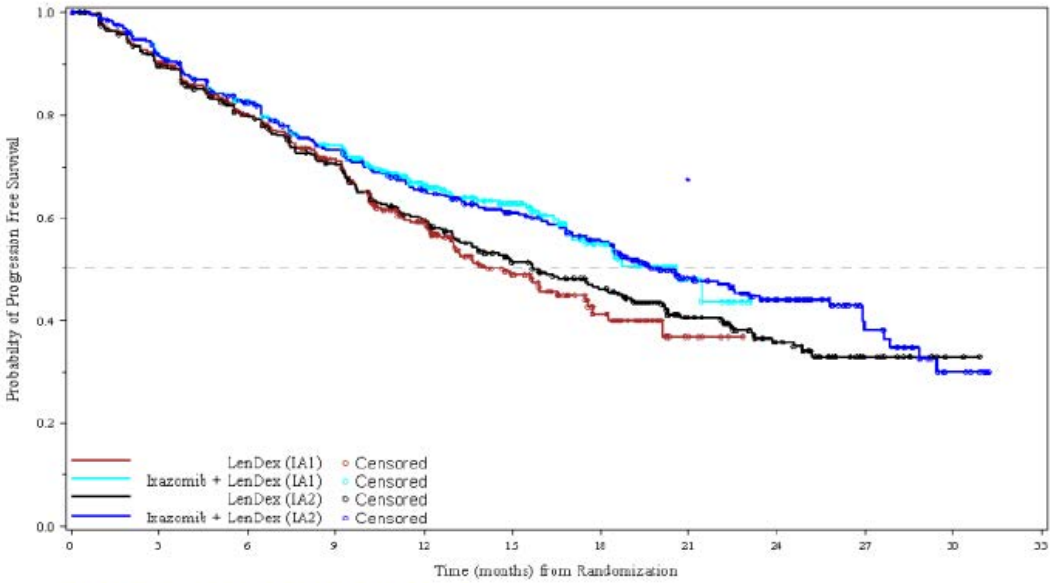
This second analysis is a non-inferential analysis of the PFS outcome. The magnitude of difference in estimated median duration of PFS was of a similar magnitude, favouring ixazomib of 4.1 months compared to placebo (that is 20.0 versus 15.9 months). However, the HR for the second analysis of PFS was 0.818 (95% CI: 0.67, 1.0), nominal p value = 0.054.

This later HR analysis result was the basis for the CHMP delivering a negative opinion for registration. However, the sponsor, in their response to request for further information by the TGA, has provided the opinion of the FDA together with supplementary analyses in order to support registration.

The evaluation of the later PFS data demonstrates a stable estimate of the median duration of PFS for the ixazomib arm at 20 months. The driver of change of the upper 95% confidence interval of HR of PFS to include 1 was assessed as a change in the estimate of PFS for the placebo arm.

The change in estimate of PFS for each arm at each analysis point is shown in Figure 5, noting that the second PFS estimate was non-inferential.

Figure 5: Changes in IRC PFS results between the primary analysis and 12 July 2015 Analysis – ITT population

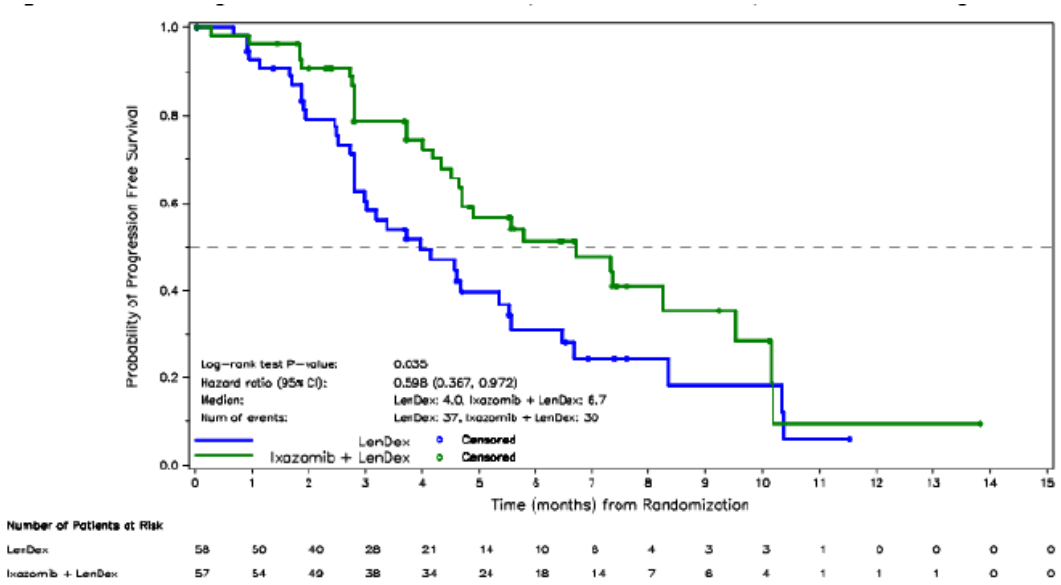


Source: Ad hoc Figure 14.3.2.1Q (12 July 2015).
Changes in IRC PFS results between the 2 time points are mainly driven by the change in the median PFS in the placebo regimen. The ixazomib regimen was consistent between the 2 time points.
IA1=primary analysis (30 October 2014); IA2=12 July 2015 analysis; IRC=independent review committee; ITT=intent-to-treat; PFS=progression-free survival.

The sponsor presented the outcomes of an extension of C16010 performed in China among 115 patients.

The baseline characteristics of the patients enrolled into this extension study are dissimilar to those in the main study, and therefore direct comparison is not possible. The estimates of PFS in each treatment arm were substantially shorter than for those presented for the main study population. However, the PFS estimate for the ixazomib arm was longer at 6.7 months compared to placebo 4.0 months, the hazard ratio of PFS remained in favour of ixazomib = 0.56 (95% CI 0.37, 0.97).

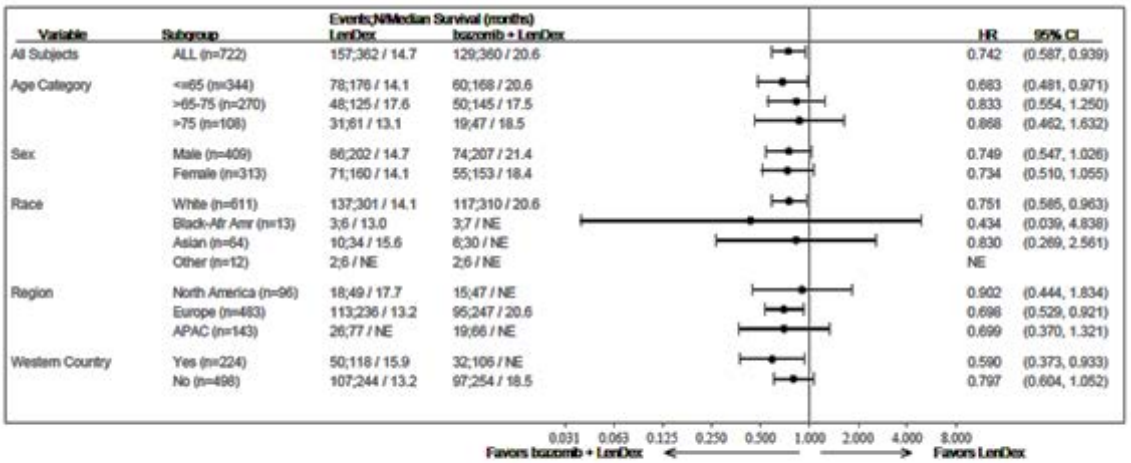
Figure 6: Kaplan-Meier plat of PFS (IRC assessments) China ITT population

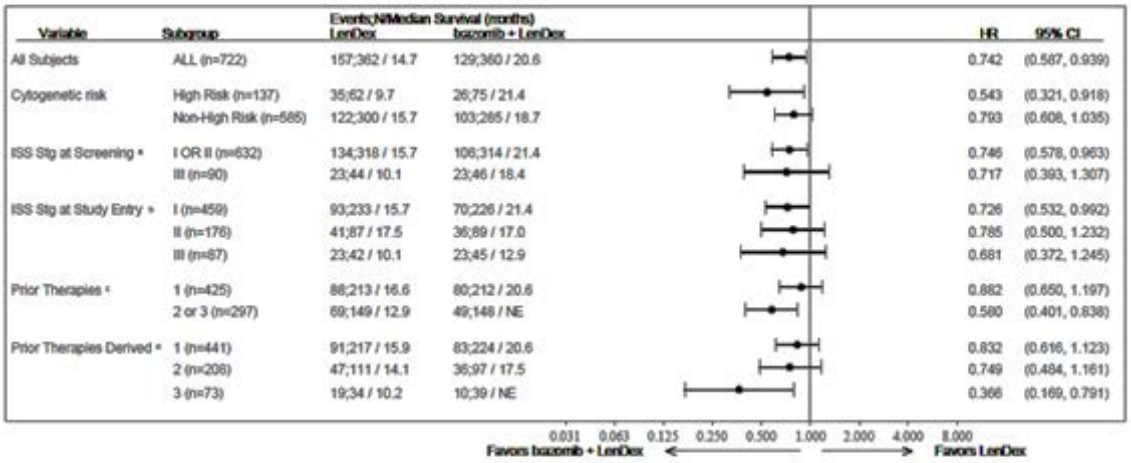


Source: C16010CH Figure 14.3.2.1A.
CI=confidence interval; IRC=independent review committee; ITT=intent-to-treat; LenDex=lenalidomide and dexamethasone.

PFS was presented according to pre-specified sub-groups, based upon the ITT population. Of note, the point estimate of PFS favoured ixazomib exposure irrespective of: prior exposure to proteasome inhibitor, prior IMID therapy, refractory status to last line of therapy as shown in Figure 7.

Figure 7: Subgroup analysis: Forest Plot of PFS ITT Population





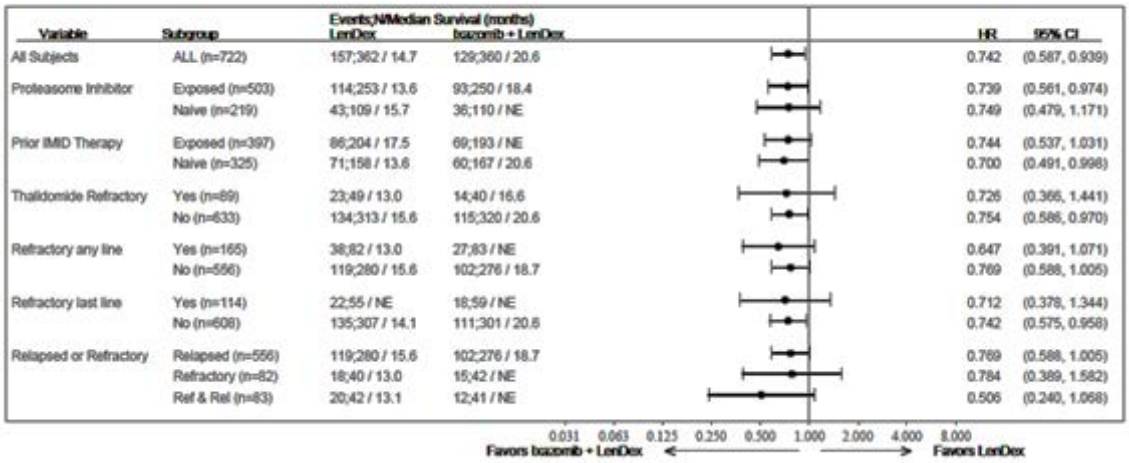
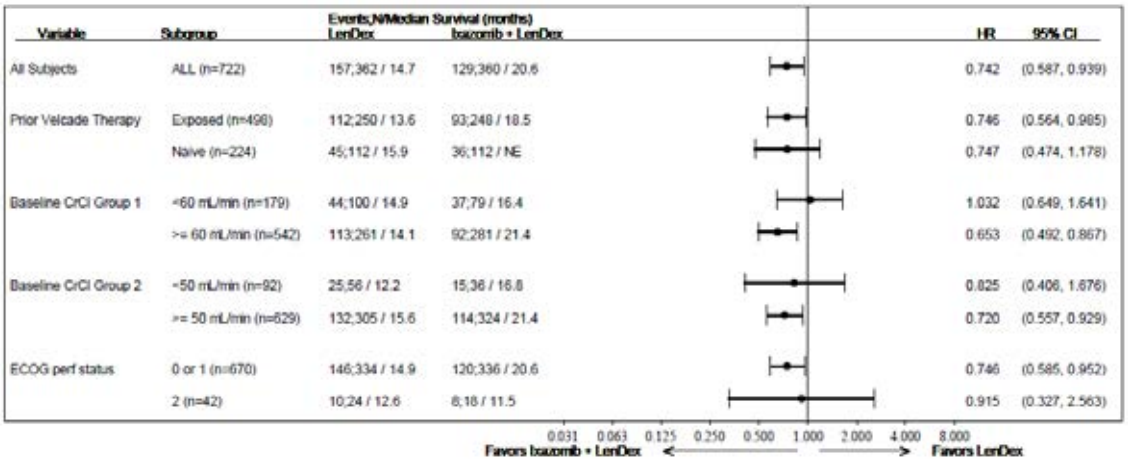


Figure 7 (continued): Subgroup analysis: Forest Plot of PFS ITT Population



Overall survival

The data for the secondary outcome of overall survival were immature at dossier submission, with approximately 15% of each arm having died. Similarly, median survival was not reached for patient harbouring del(17).

At the second pre-specified interim analysis, the estimated HR for overall survival (OS) was 0.87 (95% confidence interval: 0.64 to 1.18) based on 171 deaths, median OS was not reached for either treatment arm.

Other secondary outcomes

Independently assessed overall response rate was similar between arms - 78.3% for the ixazomib regimen and 71.5% for the placebo regimen (odds ratio = 1.44 [95% CI: 1.03, 2.03]; p = 0.035).

Patient reported outcomes (PRO) were assessed using EORTC-QLQ-C30 MY-20 and pain assessment using Brief Pain Inventory–Short Form (BPI-SF). Exposure to ixazomib did not result in a significant change in PRO scores.

Among the sub-group of patients with del(17), a smaller proportion of those receiving ixazomib had died at the 12 July 2015 cut-off 9/36, 25% as compared to those receiving placebo 15/33 (45%).

Safety

The total population having received at least one dose of oral ixazomib was 990 patients; 146 patients were exposed to at least on dose of IV ixazomib during formulation development.

Safety among three sub-populations was reported:

- The RRMM analysis population, which included all patients with RRMM who received at least 1 dose of oral ixazomib either as a single agent or in combination with other chemotherapeutic regimens (open label or unblinded; n = 572). This analysis population included patients from Studies C16003, C16004, C16010, C16013, C16015, C16020 (RRMM arm) and TB-MC010034
- The RRMM (single agent) analysis population, which included all patients with RRMM who received at least 1 dose of oral ixazomib as a single agent on a weekly or twice weekly dosing schedule (n = 127). This analysis population included patients from studies C16003, C16004, and TB-MC010034 (single agent cohort)

- The ixazomib+Len/Dex analysis population, which included all patients with MM who received at least 1 dose of oral ixazomib in combination with Len/Dex, regardless of patient population (RRMM or NDMM) (n = 539). This analysis population included patients from studies C16005, C16008, C16010, C16013, and TB-MC010034 (combination cohort).

Exposure

The median number of treatment cycles of the treatment in the safety population (n = 720) was similar in the ixazomib regimen and the placebo regimen (that is, 13.0 cycles [range: 1, 26] and 12.0 cycles [range: 1, 25 cycles], respectively). Overall, 296 (82%) patients in the ixazomib regimen and 298 (83%) patients in the placebo regimen received at least 6 cycles, while 215 (60%) patients in the ixazomib regimen and 205 (57%) patients in the placebo regimen received at least 12 cycles. There were 199 (55%) patients in the ixazomib regimen still on treatment at the first data cut-off date compared to 188 (52%) patients in the placebo regimen.

The median relative dose intensity for both ixazomib and placebo was high (97.4% ixazomib regimen; 98.2% placebo regimen).

Overall treatment emergent adverse events

The proportion of patients experiencing a TEAE was similar for ixazomib and placebo exposed patients.

Grade 3 or higher TEAE, and drug regimen related events occurred in a slightly higher proportion of patients receiving ixazomib (Table 12).

Table 12: C16010 - Overall summary of TEAEs; safety population

	n (%)	
	Placebo+LenDex N=360	Ixazomib+LenDex N=360
Any TEAE	355 (99)	351 (98)
Grade 3 or higher TEAE	221 (61)	243 (68)
Drug regimen-related TEAE[a]	317 (88)	329 (91)
Drug regimen-related Grade 3 or higher TEAE[a]	167 (46)	196 (54)
SAE	158 (44)	143 (40)
Drug regimen-related SAE[a]	83 (23)	83 (23)
TEAE resulting in dose modification of 1 or more of the 3 agents in the study drug regimen[b]	229 (64)	254 (71)
TEAE resulting in dose reduction of 1 or more of the 3 agents in the study drug regimen	160 (44)	186 (52)
TEAE resulting in discontinuation of 1 or more of the 3 agents in the study drug regimen	62 (17)	70 (19)
TEAE resulting in discontinuation of the full study drug regimen	39 (11)	46 (13)
On-study death[c]	17 (5)	12 (3)

a. TEAE assessed by the investigator as that was related to any drug in the drug combination (placebo, ixazomib, lenalidomide, or dexamethasone) was considered to be treatment related.
b. Dose modification includes dose delay, dose reduction, and drug discontinuation, the latter which could represent discontinuation of an individual drug in the combination or a discontinuation of the full treatment regimen.
c. On-study deaths are defined as deaths that occur within 30 days of the last dose of study drug.

System organ classes (SOCs) reported in ≥ 5% more patients in the ixazomib regimen than in the placebo regimen were (respectively), gastrointestinal disorders (72% versus 66%), skin and subcutaneous tissue disorders (49% versus 36%), and eye disorders (26% versus 16%). The higher frequency of TEAEs in the eye disorders SOC was accounted for by differences in low grade events denoting conjunctival irritation, such as blurred vision

(6% ixazomib regimen versus 3% placebo regimen), conjunctivitis (6% ixazomib regimen versus 1% placebo regimen), and dry eye (5% ixazomib regimen versus 1% placebo regimen).

Blood and lymphatic system disorders (SOC) were experienced by 47% of patients in the ixazomib regimen and 43% of patients in the placebo regimen, and these disorders were primarily driven by the increased frequency of thrombocytopenia in the ixazomib regimen compared to the placebo regimen (20% versus 10%, respectively).

Renal and urinary disorders (SOC) were experienced by 10% of patients in the ixazomib regimen and 17% of patients in the placebo regimen.

Deaths

A total of 29 on study deaths (within 30 days of last dose) were reported at the time of the database lock on 30 October 2014.

Five deaths were reported as being related to study drug treatment (3 in the ixazomib regimen; 2 in the placebo regimen). Drug related on study deaths reported in the placebo regimen included myocardial infarction and pulmonary embolism. In the ixazomib regimen, drug related on-study deaths included pulmonary embolism, fungal pneumonia, and coma (with concurrent diagnosis of stroke).

Treatment related SAEs

Treatment related SAEs were reported in 23% (n = 83) of patients in the ixazomib regimen and 23% (n = 83) of patients in the placebo regimen. Treatment related SAE SOCs reported in ≥ 2% of patients in either the ixazomib or placebo regimen (respectively) were infection and infestations (8% and 11%), respiratory, thoracic and mediastinal disorders (3% and 4%), blood and lymphatic system disorders (3% and 3%), gastrointestinal disorders (3% and < 1%), general disorders and administration site conditions (3% and 1%), cardiac disorders (2% and 3%), vascular disorders (2% each), metabolism and nutrition disorders (1% and 2%), and nervous system disorders (1% and 2%).

Treatment related SAEs reported in ≥ 2% of patients in either the ixazomib or placebo regimen were (respectively), pneumonia (3% versus 5%), diarrhoea (2% versus < 1%), pyrexia (2% versus 1%), and pulmonary embolism (1% versus 2%). There were no treatment related SAEs with a difference of ≥ 5 percentage points between the two treatment regimens.

Adverse events of special interest

Skeletal related TEAEs; defined as new fractures (excluding vertebral compression or rib fractures), irradiation or surgery on bone, or spinal cord compression.

There were small numbers of patients in each sub-category of skeletal related events, precluding firm conclusions being drawn.

Thrombotic events

Concomitant prophylactic thromboprophylaxis was mandated in the pivotal study, with high compliance. There was no significant increase in the incidence of thromboembolic events among patients receiving ixazomib.

Herpes zoster

Prophylactic antiviral agents were discretionary. TEAEs of herpes zoster were experienced by 20 patients (14 [4%] ixazomib regimen, 6 [2%] placebo regimen); 3 patients had events that were Grade 3 (2 ixazomib regimen, 1 placebo regimen) and none was Grade 4. Median time to herpes zoster reactivation was Cycle 6 (range Cycle 2 to 14), with 19 of the 20 patients (13 ixazomib regimen, 6 placebo regimen) receiving treatment.

New primary malignancy

Overall the incidence of second malignancies was low in each treatment arm with no predominant cancer type identified.

Other adverse events

Cardiac events

The incidence of cardiac events of clinical importance for heart failed (pooled PTs), arrhythmias (pooled PTs) and myocardial infarction (pooled PTs) showed no notable differences between the two treatment regimens. Cardiac events increased with increasing age in both treatment regimens.

Rash

No events of Stevens-Johnson syndrome or toxic epidermal necrolysis were observed. The incidence of rash (pooled PTs) was highest during the first 3 months of treatment and generally declined over time. The incidence of rash (pooled PTs) in the first 3 months of treatment was 30% (n = 109) in the ixazomib regimen and 17% (n = 61) in the placebo regimen. No grade 4 events of rash were reported.

Gastrointestinal adverse events

Ixazomib exposure was associated with an increased incidence of related nausea, vomiting and diarrhoea as compared to placebo.

Thrombocytopenia

Thrombocytopenia (pooled PTs) Grade 3 (< 50,000/mm^3 to 25,000/mm3) TEAEs were reported in 37 (10%) patients in the ixazomib regimen and 16 (4%) patients in the placebo regimen, while Grade 4 (< 25,000/mm^3) TEAEs were reported in 25 (7%) and 11 (3%) patients in the two treatment regimens, respectively. No Grade 5 TEAEs were reported in either of the two regimens.

Neutropenia

Neutropenia (all PTs) Grade ≥ 3 TEAEs were reported in 20% (n = 73) patients in the ixazomib regimen and 20% (n = 71) of patients in the placebo group, and included Grade 3 TEAEs in 16% (n = 57) and 14% (n = 51) of patients, respectively, and Grade 4 TEAES in 4% (n = 16) and 6% (n = 20) of patients, respectively.

Febrile neutropenia was reported in 9 patients (2 patients [< 1%] in the ixazomib regimen versus 7 patients [2%] in the placebo regimen). There were no discontinuations due to febrile neutropenia or concurrent infections.

Liver impairment

Events reported in ≥ 2% of the total population were ALT increased (2% [n = 6] ixazomib; 3% [n = 11] placebo), AST increased (< 1% [n = 3] ixazomib; 2% [n = 6] placebo), blood alkaline phosphatase increased (2% [n = 6] ixazomib; < 1% [n = 1] placebo).

One patient in each treatment arm had laboratory values which met the criteria for Hy's law.

Peripheral neuropathy

The incidence of any grade peripheral neuropathy was highest among patients receiving ixazomib (11% versus 9%). However the incidence of grades ≥ 3 events was similar.

Non-infectious encephalopathy

Two patients experienced related events of ≥ grade 3 encephalopathy in the ixazomib arm, whereas no events were reported among those receiving placebo.

Risk management plan

The RMP proposed by the sponsor was considered satisfactory by the RMP evaluation section, with the exception of two items relating to the PI, deferred to the Delegate – see Attachment 2.

Routine risk minimisation activities are proposed.

Risk-benefit analysis

Discussion

The single pivotal randomised controlled trial is considered sufficiently well designed to sufficiently be able to demonstrate a difference between the ixazomib + Len/Dex and Len/Dex regimens. The results of the first PFS estimates were statistically significantly different between the treatment arms and this serves as the only formal analysis of PFS.

The estimate of median duration of PFS for the placebo + Len/Dex arm of the pivotal study is consistent with the duration reported previously.

Patient reported outcomes assessed in the pivotal study demonstrated neither a benefit nor deterioration associated with ixazomib exposure. In the absence of demonstrated benefit in overall survival, the effect on PFS and patient reported outcomes have to be considered in parallel.

The first (inferential) interim analysis of the single pivotal study demonstrated a PFS benefit from the addition of ixazomib to the combination of lenalidomide and dexamethasone of 5.9 months.

The second (non-inferential) interim analysis continued to demonstrate the estimated median duration of PFS in the ixazomib arm of 20 months was stable, whereas the estimate for the placebo arm increased from 14.7 months to 15.9 months.

At the first interim analysis, the estimate of PFS plus demonstrating benefit from the addition of ixazomib was similar across pre-specified sub-groups.

The natural head to head comparison between bortezomib and ixazomib has obviously not been performed among the data presented. However, the prior use of bortezomib was not associated with a lack of efficacy of ixazomib in the pivotal study population.

The data for the secondary outcome of overall survival is immature and does not currently demonstrate a survival benefit from the use of ixazomib. The analysis of overall survival is based upon the time from randomisation of study therapy to death. This analysis is confounded by the potential for patients in the placebo arm to subsequently receive ixazomib following disease progression. This outcome cannot therefore demonstrate a survival difference solely based upon treatment with ixazomib in the study period.

The assessment of overall survival in the small number of patients with del(17) does not demonstrate a statistically significant improvement for the patients receiving ixazomib.

The overall response rate of patients in each arm was significantly different, favouring ixazomib, with approximately twice as many patients achieving a complete response in the ixazomib arm. However, no difference in time to response was observed.

Indication

In the sponsor's proposed indication, the use of the word "received" in the context of prior therapy can be plausibly taken to mean one dose of a medication, rather than a complete course of treatment.

The Delegate concurs with the amendments to the wording recommended by the clinical evaluator, to read:

> *'Patients with relapsed and/or refractory multiple myeloma whose disease has progressed on at least one prior therapy."*

Deficiencies of the data

The submission relies upon a single randomised controlled trial. While there is inconsistency in the statistical significance of the estimates of progression free survival between the two interim analysis time-points, the first time-point was pre-specified to be the only inferential test, if demonstrating a benefit to ixazomib.

Patient reported outcomes demonstrated a similarity of patient experience between the two pivotal study arms, as opposed to demonstrating superiority for those receiving ixazomib.

Relapsed/refractory multiple myeloma remains a disease characterised by further disease progression and death despite the increased number of treatment regimens available to Australian patients. In terms of overall survival the use of ixazomib does not change the therapeutic landscape.

Conditions of registration

The RMP evaluator has recommended the following wording:

Implement EU-RMP version 1.1 dated 20 January 2016 (data lock point 30 October 2014) with the Australian Specific Annex version 1.1 dated June 2016 and any future updates as agreed with the TGA.

Summary of issues

- Ninlaro is the second in class proteasome inhibitor after bortezomib. Ninlaro is the first orally bioavailable, potent, reversible, and selective small molecule inhibitor of the 20S proteasome.
- Ninlaro provides a first opportunity for a combination of all-oral therapies to be utilised in MM and does not require pre-medication or pre-hydration.
- Primary outcome of PFS demonstrates a five month advantage from ixazomib + Len/Dex over Len/Dex.
- Overall survival data remains immature, and is likely to be confounded by subsequent therapies.
- Discrepancy between the FDA and EMA registration decision.

Proposed action

The Delegate had no reason to say, at this time, that the application for ixazomib should not be approved for registration.

The advice of the committee is requested prior to a decision on registration of ixazomib.

The sponsor is kindly requested to outline the outcome of the CHMP meeting of 5th September 2016 in their pre-ACPM response, and to update the TGA with the approval status of ixazomib in other jurisdictions.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider the estimates of progression free survival from the single pivotal study sufficient to recommend registration?
2. Does the committee consider the immature overall survival data preclusion to registration?
3. What does the committee consider the population in whom ixazomib can be considered to have a positive risk-balance?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

Takeda welcomed the Delegate's proposed action to approve ixazomib for registration, although for the indication suggested by the sponsor and subsequently accepted by the clinical evaluator in the second round evaluation.

At the time, ixazomib had received regulatory approval from the US FDA (20 Nov 2015), Health Canada (4 Aug 2016), Israel Ministry of Health (14 Aug 2016), and was also approved as a Medical Service Product (MSP) in Venezuela (16 May 2016) by Venezuela Ministry of Health. Ixazomib received a negative opinion by the EU CHMP in May 2016; a re-examination appeal of the decision resulted in a positive opinion in September 2016.

In response to the specific advice sought by the Delegate, a discussion of the efficacy, safety and overall benefit-risk profile of ixazomib was presented for the Committee's consideration.

Sponsor's comment on the evaluation

Unmet clinical need

The sponsor discussed that MM remains an incurable disease with approximately one-third of patients not responding to front line therapy, and nearly all patients eventually relapsing after their previous treatment. New agents that expand treatment options for relapsed patients or that are active in patients who are refractory to current therapies and reduce toxicities and myelosuppression are needed.

Ixazomib is the first oral proteasome inhibitor. As an all-oral combination, the ixazomib+Len/Dex regimen offers several benefits over existing regimens for medical practice, patients and caregivers.

Safety and Efficacy

The results from Study C16010 demonstrate that ixazomib in combination with Len/Dex provides a statistically significant and clinically meaningful improvement in PFS and a trend for improvement in OS compared with placebo+Len/Dex. Immature OS data does not preclude registration. With the acknowledgment that OS data is important, the study continues in a double blind, placebo controlled fashion in order to obtain more mature survival data.

These data support the therapeutic use of ixazomib in patients with RRMM who have received at least 1 prior therapy. The ixazomib regimen offers the possibility of improving outcomes in patients across adverse prognostic factors and appears to particularly overcome the especially poor prognostic effect of del(17) myeloma and other high risk

cytogenetic abnormalities (t[4;14], t [14;16]) offering a much needed therapy to patients who have a particularly high unmet need.

Importantly, ixazomib in combination with Len/Dex did not substantially increase toxicity, add to or increase the toxicity of the background regimen; the TEAEs were consistent with the reported safety profiles of the individual agents in the combination regimen and were tolerable and clinically manageable. QoL was maintained despite the addition of a third drug, and ixazomib provides the convenience of an all-oral proteosome inhibitor/immunomodulator combination therapy for patients with RRMM.

Post-marketing data

Since ixazomib's launch in the US in December 2015, the total patient-years of exposure are estimated to be approximately 531 (20 November 2015 to 19 May 2016). To date, data in the post-marketing setting are consistent with the safety profile seen during clinical development. In the period up to the 19 May 2016 there has been no new significant safety information that affects the overall positive benefit-risk for ixazomib in combination with Len/Dex in the treatment of patients with MM who have received at least 1 prior treatment.

Benefit-risk

In a RRMM patient population representative of 'real world' patients, the ixazomib regimen is effective at improving PFS (median 20.6 months), has high response rates with clinically meaningful durability, adds little clinically significant toxicity, and maintains QoL compared with the Len/Dex background therapy. The estimated size of the treatment effect of ixazomib is clinically significant, meaningful, and valuable. Additionally, the study population was generally unselected, including patients with either cardiac risk factors or with impaired renal function, which allowed the establishment of the benefit-risk profile in these subgroups.

Indication

Takeda proposes the following indication for ixazomib:

> *'for the treatment of patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy'.*

This indication was suggested by Takeda and subsequently accepted by the clinical evaluator at the second round evaluation.

Conclusion

Takeda welcomed the Delegate's proposed action to approve ixazomib for registration.

Even with an increase in the number of therapeutic options for patients with RRMM, the disease remains incurable. Nearly all patients eventually experience disease relapses and require further therapy; therefore, in this life-threatening disease, there is a need for new and better agents that provide prolonged disease control while maintaining QoL.

Ixazomib demonstrates a positive benefit-risk profile with a simple and convenient all-oral treatment option, which is more suitable to prolonged administration.

Advisory Committee Considerations

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ninlaro ixazomib citrate 4 mg, 3 mg and 2.5 mg capsules of to have an overall positive benefit–risk profile for the amended indication;

> *Ninlaro is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy.*

In making this recommendation the ACPM

- noted that Ninlaro was the only oral agent in its class
- was of the view that ixazomib citrate demonstrated reasonable efficacy for the proposed indication without significant safety concerns.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

The committee is requested to provide advice on the following specific issues:

1. *Does the committee consider the estimates of progression-free survival from the single pivotal study sufficient to recommend registration?*

The committee was of the view that the pivotal study was well designed with an adequate population and the statistically significant reduction of progression free survival (PFS) was a robust endpoint sufficient for product registration.

2. *Does the committee consider the immature overall survival data preclusion to registration?*

The committee considered that the immature survival data does not preclude registration and noted that the 'EMA guideline on the evaluation of anticancer medicinal products in man' outlines progression free survival as an acceptable primary endpoint.

3. *What does the committee consider the population in whom ixazomib can be considered to have a positive risk-balance?*

The committee noted that ixazomib citrate has a positive risk balance in patients with multiple myeloma which has relapsed or progressed as shown by the population of the pivotal efficacy study.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ninlaro ixazomib (as citrate) 4 mg, 3 mg and 2.5 mg capsule, indicated for:

> *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.*

Attachment 1. Product Information

The PI for Ninlaro approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

Attachment 2. Extract from the Clinical Evaluation Report

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