



European Medicines Agency review of ixazomib (Ninlaro) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

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ABSTRACT

On 21 November 2016, the European Commission issued a marketing authorisation valid throughout the European Union for ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Ixazomib was evaluated in one, randomised, double-blind, phase III study comparing ixazomib plus lenalidomide and dexamethasone (n=360; ixazomib arm) versus placebo plus lenalidomide and dexamethasone (n=362; placebo arm) in adult patients with relapsed and/or refractory multiple myeloma who had received at least one prior therapy. The median progression-free survival (PFS) in the intent-to-treat population was 20.6 months in patients treated with ixazomib compared with 14.7 months for patients in the placebo arm (stratified HR=0.742, 95% CI 0.587 to 0.939, stratified p-value=0.012). The most frequently reported adverse reactions (≥20%) within the ixazomib and placebo arms were diarrhoea (42% vs 36%), constipation (34% vs 25%), thrombocytopenia (28% vs 14%), peripheral neuropathy (28% vs 21%), nausea (26% vs 21%), peripheral oedema (25% vs 18%), vomiting (22% vs 11%) and back pain (21% vs 16%). The scientific review concluded that the gain in PFS of 5.9 months observed with ixazomib was considered clinically meaningful. Concerning the possible uncertainty about the magnitude of the effect, this uncertainty was acceptable given the favourable toxicity profile, and considering that ixazomib is the first agent to allow oral triple combination therapy in this patient population which represents a therapeutic innovation in terms of convenience for patients. Therefore, the benefit–risk for ixazomib in combination with lenalidomide and dexamethasone was considered positive, although the efficacy evidence was not as comprehensive as normally required.

BACKGROUND

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterised by the accumulation of clonal plasma cells in the bone marrow (and other organs), bone

lesions, anaemia and less frequently by hypercalcaemia. Other more frequent complications are infections, pain, renal impairment and neurological symptoms. MM constitutes approximately 1% of all reported neoplasms and approximately 13% of haematological cancers worldwide.¹ The estimated incidence of MM affected 35 309 individuals (19 023 males and 16 286 females) in the European Union (EU-28) in 2015² with a median age at diagnosis of 72 years.¹ The overall median survival has improved markedly, likely due to new therapy principles and the usage of new drugs; at present it is 5–6 years from diagnosis of MM.³

At the time of the marketing authorisation (MA) of ixazomib, treatment options for refractory/relapsed MM (RRMM) included bortezomib-based and lenalidomide-based regimens used in combination with corticosteroids, to which sometimes also an alkylator or an anthracycline is added.⁴ In this setting, for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent (IMiD), and have shown relapsed or refractory disease, pomalidomide (in combination with dexamethasone) and panobinostat (in combination with bortezomib and dexamethasone) are approved agents in the EU. Daratumumab a monoclonal antibody, was also approved in the EU for the treatment of adult patients with relapsed and refractory MM whose prior therapy included a proteasome inhibitor and an IMiD and who have demonstrated disease progression on the last therapy. The proteasome inhibitor carfilzomib and the monoclonal antibody elotuzumab both in

Table 1 Steps in the initial evaluation and the re-examination of the marketing authorisation for Ninlaro

Step/procedure	Date
Accelerated assessment procedure agreed	23 July 2015
Initial marketing authorisation application received	30 July 2015
Adoption of the consolidated list of questions by the CHMP	17 December 2015
Submission of responses to the consolidated list of questions to the CHMP	25 January 2016
Outstanding issues were addressed by the applicant during an oral explanation at the CHMP	30 March 2016
The CHMP adopted a negative opinion for granting a marketing authorisation to Ninlaro	26 May 2016
The re-examination procedure started	21 August 2016
SAG meeting	5 September 2016
The CHMP adopted a positive opinion for granting a marketing authorisation to Ninlaro	15 September 2016

CHMP, Committee for Medicinal Products for Human Use; SAG, Scientific Advisory Group.

combination with lenalidomide and dexamethasone were approved in the EU for the treatment of adult patients with MM who have received at least one prior therapy. Ixazomib is an oral, highly selective and reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome which leads to the disruption of cellular regulatory mechanisms further resulting in inhibition of cell growth and survival pathways and induction of apoptosis.

The recommended starting dose of ixazomib is 4mg administered orally once a week on days 1, 8 and 15 of a 28-day treatment cycle.

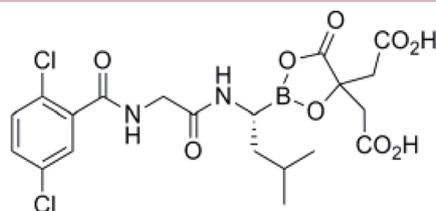
The applicant submitted an application for MA to the European Medicines Agency (EMA) in July 2015 requesting the approval for the following indication: 'Ninlaro is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.'

The review of this new drug application was conducted by the EMA Committee of Human Medicinal Products (CHMP). The CHMP recommended the granting of a conditional marketing authorisation for ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy. Table 1 presents a summary

of key regulatory steps and procedures for Ninlaro. The objective of this paper is to summarise the scientific review of the application leading to regulatory approval of ixazomib in the EU. A conditional approval is reserved for medicinal drugs that treat, prevent or diagnose seriously debilitating diseases or life-threatening diseases, or rare diseases (orphan medicinal products) or drugs to be used in emergency situations in response to threats. With this approval, the applicant company is obliged to submit additional data, with a view to confirming that the benefit–risk balance is positive. A conditional approval is only valid for 1 year but can be renewed. The renewal is given on the basis of the confirmation of the benefit–risk balance, taking into account the specific obligations and the timeframe for their fulfilment. Once it is judged that remaining data have been provided or are no longer required, the approval can be converted to a 'standard' approval. If at any time the benefit–risk is considered to be negative, the marketing authorisation can be suspended or revoked.

Non-clinical aspects and clinical pharmacology

Ixazomib citrate, a prodrug, is the drug substance that rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib (figure 1). Ixazomib is an oral, highly selective and reversible proteasome



Molecular formula: C₂₀H₂₃BCl₂N₂O₉

Relative molecular mass: 517.12 g/mol.

The chemical name of ixazomib citrate is 2-[(1R)-1-[[2-[(2,5-dichlorobenzoyl) amino]acetyl]amino]-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diacetic acid

Figure 1 Molecular structure of ixazomib citrate.

inhibitor which preferentially binds and inhibits the chymotrypsin-like activity of the $\beta 5$ subunit of the 20S proteasome. Ixazomib treatment of an MM cell line resulted in caspase-mediated apoptosis, accompanied by induction of the unfolded protein response, increases in several pro-apoptotic BH3-only proteins and an apoptotic cascade. In vitro, ixazomib has shown antitumour activity against additional cultured human MM cells, and activity was also evidenced in purified MM cells (CD138+) from patients, including those that had relapsed after multiple prior therapies, including bortezomib, lenalidomide and dexamethasone.⁵ In vitro synergy between ixazomib and lenalidomide was detected in 2 of 4 MM cell lines evaluated in viability assays, and the other 2 MM cell lines evaluated showed additivity of the combination.

In multicycle repeated-dose toxicity studies conducted in rats and dogs, the principal target organs included the gastrointestinal tract, lymphoid tissues and the nervous system. In the 9-month study (10 cycles) in dogs orally administered with a dosing schedule mimicking the clinical regimen (28-day cycle), microscopic neuronal effects were generally minimal in nature and only observed at 0.2 mg/kg (4 mg/m²). The majority of target organ findings were partially or fully recovered following discontinuation of treatment, with the exception of neuronal findings in the lumbar dorsal root ganglion and dorsal column.

Ixazomib is not mutagenic or clastogenic. In pregnant rats and rabbits ixazomib caused embryo-fetal toxicity only at maternally toxic doses and at exposures that were slightly higher than those observed in patients receiving the recommended dose. In the pregnant rat dose range finding study, there were decreases in fetal weights and a trend towards decreased fetal viability and increased post implantation losses; however, these findings were not reproduced in the definitive study (no observed adverse effect level (NOAEL) for rat embryo fetal parameters ≥ 0.6 mg/kg). In pregnant rabbits, ixazomib caused embryo-fetal lethality and postimplantation loss in a dose range-finding study at 1 mg/kg; however, these findings were not clearly reproduced in a definitive study at the same dose. In the definitive study, increases in fetal external abnormalities in the tail were observed at doses ≥ 1.0 mg/kg, and skeletal variations/abnormalities were observed at doses ≥ 0.3 mg/kg. The NOAEL was 0.1 mg/kg for rabbit embryo-fetal development. Thus, ixazomib is not recommended during pregnancy as it can cause fetal harm when administered to a pregnant woman.

No dose adjustment of ixazomib is required for patients with mild hepatic impairment and patients with mild or moderate renal impairment based on the results of a population pharmacokinetic (PK) analysis. However, the reduced dose of 3 mg is recommended in patients with moderate or severe hepatic impairment and in patients with severe renal impairment since unbound dose-normalised area under the curve (AUC) was 27% and 38% higher in these groups compared with patients with normal hepatic and renal function, respectively.

In a clinical study, ixazomib C_{max} and area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration (AUC_{0-last}) were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended. When ixazomib is administered together with dexamethasone, the risk for reduced efficacy of oral contraceptives needs to be considered.

Clinical efficacy

The MA application was based on one pivotal study (study C16010). This was a phase III, prospective and randomised, double-blind study of ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory MM.⁶

Eligibility criteria included patients with RRMM who had received one to three prior therapies including: relapsed from previous treatment(s) but were not refractory to any previous treatment; refractory to all lines of previous treatment(s); and relapsed from at least one previous treatment and additionally were refractory to at least one previous treatment. Refractory disease was defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy. Patients who progressed after 60 days from the last dose of a given therapy were considered relapsed.

Ixazomib 4 mg was to be administered on days 1, 8 and 15 in combination with lenalidomide 25 mg on days 1–21 and dexamethasone 40 mg on days 1, 8, 15 and 22 in 28 days cycles until progressive disease or unacceptable toxicity. This dosing regimen of ixazomib was based on Studies C16003 and C16004 which were phase 1, open-label, dose-escalation studies evaluating the safety, maximum tolerated dose and activity of single-agent oral ixazomib in adult patients with RRMM.^{7,8} The dosing regimen of the combination was based on study C16005 an open-label, multicentre clinical trial evaluating ixazomib oral in combination with Lenalidomide and dexamethasone in patients with newly diagnosed MM.⁹ The primary efficacy endpoint was progression-free survival (PFS) in the intend-to-treat (ITT) population defined as the time from the date of randomisation to the date of first documentation of disease progression, based on central laboratory results and international myeloma working group (IMWG) criteria,¹⁰ or death due to any cause, whichever occurred first.

A total of 722 patients were randomly allocated (1:1 ratio) to receive either ixazomib or placebo in combination with lenalidomide and dexamethasone and they were stratified by: prior therapies (1 vs 2 or 3); previous exposure to proteasome inhibitors (naive vs exposed) and International Staging System disease stage (I or II vs III).

At the first and predefined interim analysis which was carried out with 286 independent review committee (IRC)-assessed events (data cut-off date 30 October 2014)

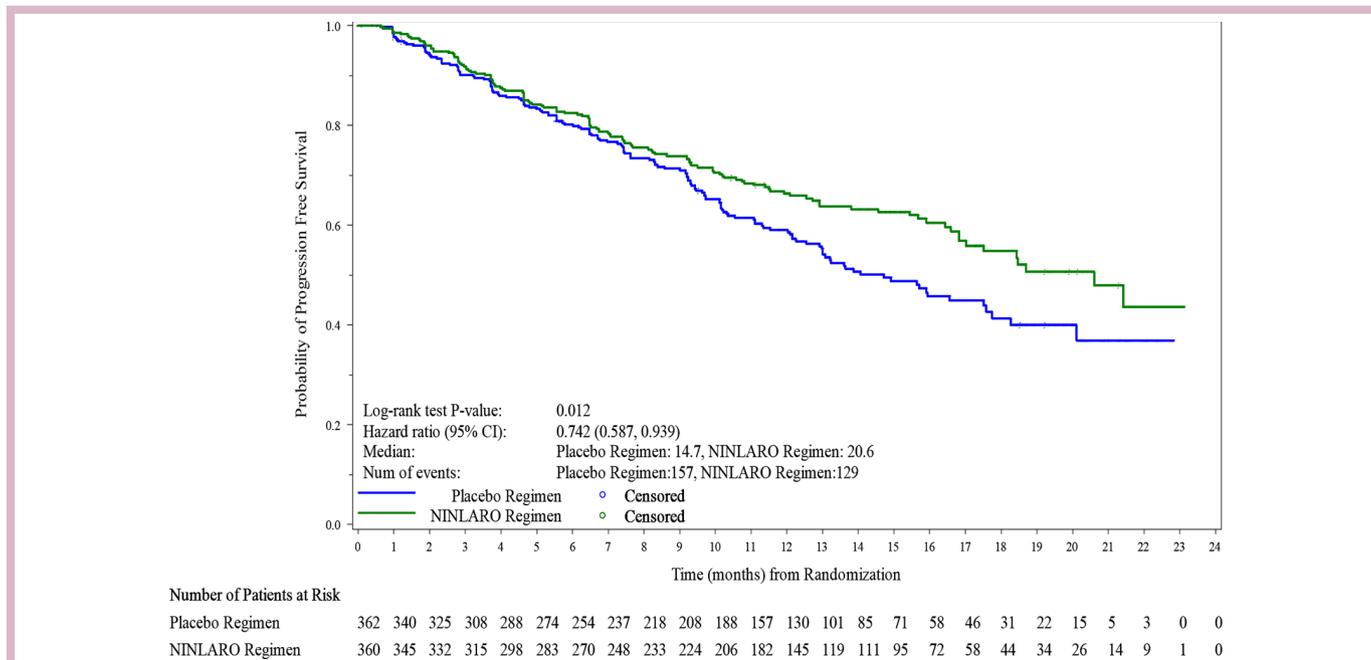


Figure 2 Kaplan-Meier plot of progression-free survival on independent review committee assessment in the intent-to-treat population (Study C16010)-data cut-off 30 October 2014.

the median PFS was 20.6 months in patients treated with ixazomib+lenalidomide+dexamethasone arm compared with 14.7 months for patients in the placebo +lenalidomide+dexamethasone arm (stratified HR=0.742, 95% CI 0.587 to 0.939, stratified p value=0.012) (figure 2). At the second interim analysis which was carried out with 372 IRC-assessed events (data cut-off date 12 July 2015), the median PFS was 20.0 months in ixazomib arm compared with 15.9 in the placebo arm (HR=0.818, 95% CI 0.67 to 1.0, p=0.054).

The median overall survival (OS) had not been reached with either treatment regimen at the time of the first or second interim analysis (22% and 35% of the pre-specified events required for the final OS analysis reported, respectively).

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

A summary of key favourable effects is displayed in table 2.

Clinical safety

In study C16010, the median number of ixazomib or placebo treatment cycles was 12.0 in both the ixazomib (range, 1–26 cycles) and placebo (range, 1–25 cycles) arms, respectively. The median numbers of treatment cycles for lenalidomide and dexamethasone was 13.0 (range, 1–26) in the ixazomib arm and 12.0 (range, 1–25) in the placebo arm. The median dose intensity was 97.4% for ixazomib and 98.2% for placebo, 93.8% and 95.6% for lenalidomide (ixazomib and placebo arms respectively) and 92.8% and 95.0% for dexamethasone (ixazomib and placebo arms respectively).

The incidence of grade 3 or higher TEAE was 74% in the ixazomib arm and 69% in the placebo arm. Serious adverse events occurred in 47% of patients in the ixazomib arm and 49% of patients in the placebo arm. A total of 38 on-study deaths (within 30 days of the last dose of study drug) were reported in Study C16010: 15 (4%) in the ixazomib arm and 23 (6%) in the placebo arm.

Important identified risks included thrombocytopaenia, severe gastrointestinal events (specifically nausea, vomiting and diarrhoea) and peripheral neuropathy. Missing information included long term safety and safety regarding the use of ixazomib during pregnancy and lactation.

A summary of key unfavourable effects is displayed in table 2.

DISCUSSION AND BENEFIT-RISK ASSESSMENT

Initially, the applicant applied for an indication in MM patients who have received at least one prior therapy. The CHMP considered that although the result at the preplanned first interim PFS analysis (p=0.012) achieved the prespecified threshold for claiming benefit at this milestone (p<0.0227) and the treatment benefit was considered to be clinically relevant, the statistical result was not considered sufficiently robust, given that this was a single pivotal trial (a single trial would need to achieve p<0.00125 to replicate the evidence from two trials positive at p<0.05). In addition, efficacy data from the second interim analysis, showed a reduced difference in effect between arms in the overall ITT population for PFS, response rates and time to progression compared with the previous analysis.

Table 2 Key favourable and unfavourable effects for ixazomib in combination with lenalidomide and dexamethasone versus placebo in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy

	Effect	Short description	Unit	Ixazomib+LenDex	Placebo +LenDex	Uncertainties/strength of evidence
Favourable*	PFS (median)	Time from randomisation to first documentation of disease progression or death due to any cause.	Months	20.6 (17.02, NE)	14.7 (12.91, 17.58)	HR of 0.742 (95% CI 0.587 to 0.939) p=0.012; some uncertainty about the magnitude of the treatment effect.
	OS† (median)	Time from randomisation to death.	Months	NE	NE	HR of 0.868 (95% CI:0.642 to 1.175) p=0.359; immature data.
	ORR	Proportion of ITT patients who achieved PR or better.	%	78.3 (73.7, 82.5)	71.5 (66.6, 76.1)	
Unfavourable†	Thrombocytopenia	Grade ≥3 ADRs	%	19	9	No uncertainties
	Nausea	Grade ≥3 ADRs	%	2	0	
	Vomiting	Grade ≥3 ADRs	%	1	<1	
	Diarrhoea	Grade ≥3 ADRs	%	6	3	
	Peripheral neuropathy	Grade ≥3 ADRs	%	2	2	

*Data cut-off:30 October 2014.

†Data cut-off: 12 July 2015.

ADRs, adverse reactions; ITT, intent-to-treat; LenDex, lenalidomide and dexamethasone; NE, not estimated; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

The applicant company argued that the first interim analysis of Study C16010 was the primary analysis for PFS and, as prespecified stringent criteria of statistical significance had been met and on the basis of preliminary analyses and a review of the literature, there is a rationale for the subgroup of patients with at least two prior therapies to be associated with increased sensitivity to ixazomib because of a number of factors, including the clinical features of these patients and the evolution of MM clones that are likely more sensitive to proteasome inhibitors.

A scientific advisory group was convened by CHMP to provide advice on the basis of the grounds for re-examination submitted by the company. The group advised that on the basis of the primary PFS analysis, which was conducted according to the pre-specified statistical considerations, a statistically and clinically significant improvement in PFS has been observed. The fact that a subsequent exploratory analysis showed some uncertainty about the level of statistical significance was not enough to change the conclusion about a clear beneficial effect in terms of PFS on the basis of the preplanned analysis.

Taking into account the expert advice, scientific assessment of the data and argumentations, the CHMP acknowledged that the second interim analysis should be interpreted as secondary and concluded that it was difficult not to acknowledge the positive result in a large clinical trial in this clinical setting. In the pivotal trial, the

median OS was not evaluable yet and the data were considered immature in this respect. The efficacy evaluation was primarily based on assessment of PFS and requires verification of the effect on OS. Therefore, the CHMP considered that further OS analysis with longer follow-up is needed from the study C16010 in order to confirm the favourable trend in OS with ixazomib regimen.

Based on the above, the CHMP concluded that the benefit–risk for ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy was considered positive. However, it was also considered that the efficacy evidence was not as complete as normally expected and that there was a need to further confirm the benefit–risk of ixazomib in the approved indication, in particular, concerning the consistency of treatment effect across different treatment lines. Therefore, a conditional MA was recommended. The applicant committed to provide comprehensive clinical data from three phase III randomised studies (Study C16010 China Continuation, C16014 and C16019) and one global, prospective, non-interventional, observational study (Study NSMM-5001). These data were expected to provide evidence of the extent of efficacy of ixazomib across the spectrum of patients with newly diagnosed MM and address any remaining uncertainties about the consistency of treatment effect across different treatment lines.

The results from the C16010 China continuation study of the same study design as the C16010 global study were submitted post-approval and showed a positive treatment effect of ixazomib for the primary endpoint PFS consistent with the results of the pivotal global study C16010 together with a survival benefit. Results from study C16019 and results from study C16014 are expected to be made available by December 2020.

In the context of the increasingly complex treatment landscape that is attributable to an improved understanding of the disease biology and an increase in available therapies, including immunotherapy, monoclonal antibodies and CAR T cell technology, myeloma may become either curable or a chronic disease with long survival. Ixazomib can be combined with existing treatments and may be considered when treating patients with relapsed and/or refractory MM. Ixazomib is the first agent to allow oral triple combination therapy in this patient population, which represents a therapeutic innovation in terms of convenience for patients. The EMA will review the benefit/risk and new information about ixazomib on an annual basis. Up to date information on this medicinal product is available on the website of the EMA (<http://www.ema.europa.eu>).

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