

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208462Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur
Subject	Office Director Summary Review
NDA/BLA #	208462
Applicant Name	Takeda/Millennium, Inc.
Date of Submission	July 10, 2015
PDUFA Goal Date	March 10, 2016
Proprietary Name / Established (USAN) Name	Ninlaro/ixazomib
Dosage Forms / Strength	4 mg, 3 mg and 2.3 mg capsules
Proposed Indication(s)	a proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Division Director Review	Ann Farrell, MD
Regulatory Project Manager Review	Jacquie Jones, MS, BSN
Medical Officer Review	Alexandra Schwarsin, MD/Angelo DeClaro, MD,
Statistical Review	Yun Wang, PhD /Lei Nie, PhD/ Raji Sridhara, PhD
Pharmacology Toxicology Review	Emily Place, PhD/Christopher Sheth, PhD/John Leighton, PhD
CMC Review/Microbiology	Janice Brown, BS, MS/Olen Stephens, PhD and the team
Clinical Pharmacology Review	Vicky Hsu, PhD/Jee Eun Lee, PhD/Dinko Rekić, PhD/Bahru Habtemariam, PharmD/Nitin Mehrotra, PhD
OSI	Anthony Orenca, MD/Susan Thompson, MD for Janice Pohlman, MD, MPH/Kassa Ayalew, MD, MPH
CDTL Review	Angelo DeClaro, MD
OSE	Todd Bridges, RPh/Kevin Wright/LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Sharon R. Mills, BSN, RN, CCRP/Nisha Patel, PharmD/ Amarilys Vega, MD, MPH/ Naomi Redd, PharmD/Cynthia LaCivita, PharmD/Ebony Ayres, PharmD/ Yelena Maslov, PharmD/Lubna Merchant, MS, PharmD

1. Introduction & Background

On July 10, 2015, Millennium Pharmaceuticals, Inc., submitted an NDA for Ninlaro (ixazomib) capsules, an orally bioavailable, small molecule inhibitor of the 20S proteasome, for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. The primary support for Ninlaro is based on results from a double-blind, randomized controlled trial entitled: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 plus Lenalidomide and Dexamethasone Versus Placebo plus Lenalidomide and Dexamethasone in Adult Patients with Relapsed and/or Refractory Multiple Myeloma. This application was given priority review. Ninlaro is not approved in any country at this time.

Multiple myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant cured of their disease. The development and approval of proteasome inhibitors and thalidomide analogues has improved the outlook for patients with multiple myeloma with a current median overall survival (OS) of approximately 5 years.

2. CMC/Device

There are no issues that would preclude approval from a CMC perspective, and CMC has provided an overall acceptability recommendation of the manufacturing of the drug substance and drug product. Based on the CMC review, *Ninlaro (ixazomib) capsules for oral use contain 4, 3 or 2.3 mg of ixazomib equivalent to 5.7, 4.3 or 3.3 mg of ixazomib citrate, respectively.*

The product shelf life recommendation is for 36 months when stored below 30° C. Stability studies were conducted at long-term conditions of 5°C, 25°C/60% RH and 30°C/75% RH, and an accelerated storage condition, 40°C/75% RH. The recommendation is for storage at room temperature at ICH climatic zones I, II, III, and IV.

3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. Based on the secondary review:

Ixazomib is a small molecule reversible inhibitor of the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome, being developed as a treatment for patients with multiple myeloma who have received at least one prior therapy...

The pharmacology and toxicology studies reviewed included primary pharmacodynamics, genotoxicity, safety pharmacology, repeat dose toxicology (6-month rat and 9-month dog), and embryo-fetal developmental toxicity in rats and rabbits. With regards to the pharmacology of ixazomib, the drug induced apoptosis of multiple myeloma cell lines in vitro and demonstrated 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. Additionally, ixazomib demonstrated antitumor activity in vivo in a mouse multiple myeloma tumor xenograft model. The Established Pharmacological Class of "proteasome inhibitor" was determined to be both scientifically valid and clinically meaningful for ixazomib.

*In multi-cycle general toxicity studies conducted in dogs, the principal target organs included the nervous system. Nervous system effects were primarily seen in dogs at oral doses greater than or equal to 0.1 mg/kg (2 mg/m²) and included microscopic findings of minimal to mild neuronal degeneration of the sympathetic, dorsal root, peripheral autonomic (salivary gland), end organ ganglia, and minimal secondary axonal/nerve fiber degeneration of the peripheral nerves and ascending tracts in the dorsal columns of the spinal cord. In the 9-month study (10 cycles) in dogs where the dosing regimen mimics 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; AUC₀₋₁₆₈ = 1940 hr*ng/mL). The majority of target organ findings (e.g., in the gastrointestinal tract, lymphoid tissue, and nervous system) partially or completely recovered following discontinuation of treatment, except for the neuronal findings in the lumbar dorsal root ganglion and dorsal column.*

The Applicant's proposal for Section 8 of the label is consistent with the Pregnancy and Lactation Labeling Rule. Ninlaro can cause fetal harm based on the mechanism of action and findings in animals. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures similar to those observed in patients receiving the recommended dose. Developmental toxicity studies in rats and rabbits did not show direct embryo-fetal toxicity below maternally toxic doses of ixazomib. Females of reproductive potential should avoid becoming pregnant while being treated. Fertility studies were not conducted with ixazomib; however there were no effects due to ixazomib treatment on male or female reproductive organs in studies up to 6-months duration in rats and up to 9-months duration in dogs.

No carcinogenicity studies have been conducted with ixazomib. Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay) nor was it clastogenic in a bone marrow micronucleus assay in mice. Ixazomib showed clastogenic activity (structural chromosomal aberrations) in the in vitro chromosomal aberration assay in human peripheral blood lymphocytes in the presence or absence of an exogenous metabolic activation system. Ixazomib was negative in an in vivo comet assay in mice, as assessed in the stomach and liver.

4. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval from a clinical pharmacology perspective. The following is from the clinical pharmacology review:

Exposure-response (E-R) analyses

The results of the E-R analyses for efficacy did not show a relationship between ixazomib systemic exposure and clinical response or PFS. However, results of E-R analyses for safety showed significant relationships between ixazomib systemic exposure and select AEs (rash, thrombocytopenia, diarrhea) indicating that sponsor's recommendations of dose reduction to manage these adverse events are acceptable. Ixazomib systemic exposure was not found to be a significant predictor of time to first dose reduction (p-value =0.069).

ADME

The absolute bioavailability of ixazomib is estimated to be 58%. Following oral administration, ixazomib is rapidly absorbed with a median TMAX of 1 hour. It is highly bound to human plasma proteins at 99% with a blood-to-plasma ratio of 10. Mass balance evaluation showed that approximately 62% and 22% of the radiolabeled dose were recovered, respectively, in the urine and feces. Of those in the urine, only 3% was recovered as the unchanged drug. Metabolite profiling from the mass balance study was not complete at the time of NDA submission. In vitro metabolism studies show non-CYP and CYP enzymes contribute to ixazomib metabolism. Ixazomib has a half-life of about 10 days and systemic clearance of 1.9 L/h with minimal renal clearance (6%). Based on population PK analysis, ixazomib is dose-proportional in the dose range of 0.2 to 10.6 mg.

Hepatic and Renal Impairment

No dose adjustment is needed for patients with mild hepatic impairment or mild/moderate renal impairment, based on population PK analyses of Phase 3 data. However, dose reductions to 3 mg are recommended in patients with moderate/severe hepatic impairment or severe renal impairment/end stage renal disease requiring dialysis, based on clinical studies showing ~13-42% systemic exposure increases in these groups.

Drug-Drug Interactions (DDIs)

The contribution of CYP enzymes in the biotransformation of ixazomib is 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8), 2C9 (<1%) at supra-therapeutic concentrations. Clinical DDI studies with strong CYP3A4 inhibitors ketoconazole (when accounting for period effect) and clarithromycin did not show clinically meaningful effects on ixazomib PK. However, clinical study with strong CYP3A4 inducer rifampin showed significant decrease in ixazomib exposure (AUC ↓74%, CMAX ↓54%). To avoid sub-therapeutic ixazomib concentrations, concomitant use of strong CYP3A4 inducers should be avoided. Ixazomib was not identified as a reversible or time-dependent inhibitor or inducer of CYP enzymes or any major drug transporters. It was identified as a low affinity substrate of P-gp transporter.

The review team also noted:

A previous QT-IRT review did not find clear dose- or exposure-QTc relationship for ixazomib.

5. Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

This application was supported by a multicenter, randomized, double-blind, placebo-controlled trial enrolling 722 patients with multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized in a 1:1 ratio to either the combination of ixazomib, lenalidomide and dexamethasone (n=360) or the combination of placebo, lenalidomide and dexamethasone (n=362). Patients continued treatment until disease progression or unacceptable toxicity. The trial's primary endpoint was PFS with overall survival (OS) as a key secondary endpoint.

The trial showed a statistically significant improvement in PFS. The median PFS on the combination arm of ixazomib, lenalidomide and dexamethasone was 20.6 months (95% CI: 17.0, NE) compared to a median PFS of 14.7 months (95% CI: 12.9, 17.6) on the combination arm of placebo, lenalidomide and dexamethasone (PFS HR 0.74, 95% CI: 0.59, 0.94; p value=0.012).

Table 1: Progression-Free Survival and Response Rate

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

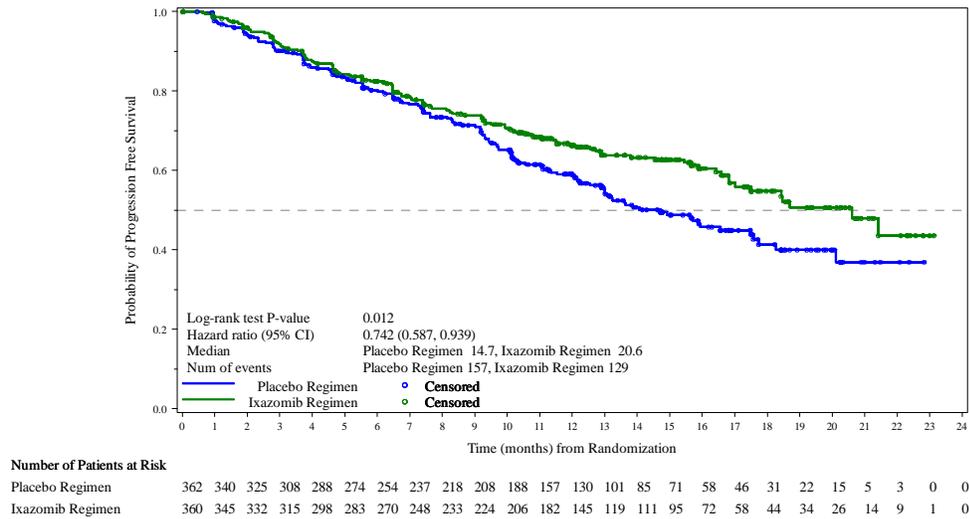
NE: Not evaluable.

*Hazard ratio is based on a stratified Cox's proportional hazard regression model. A hazard ratio less than 1 indicates an advantage for the NINLARO regimen.

†P-value is based on the stratified log-rank test.

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

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



A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. Hazard ratio of PFS was 0.82 (95% confidence interval [0.67, 1.0]) for NINLARO regimen versus placebo regimen, and estimated median PFS was 20 months in the NINLARO regimen and 15.9 months in the placebo regimen. At the same time, a planned interim OS analysis was conducted with 35% of the required number of deaths for final OS analysis; there were 81 deaths in the NINLARO regimen and 90 deaths in the placebo regimen. An OS benefit was not demonstrated.

7. Safety

The most common adverse reactions ($\geq 20\%$) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. The major safety issues requiring a warning in the labeling are thrombocytopenia, gastrointestinal toxicity, potential for embryo-fetal toxicity, peripheral neuropathy, peripheral edema, cutaneous reactions, and hepatotoxicity. See product labeling for a full description of safety.

8. Advisory Committee Meeting

No clinical efficacy or safety issues arose that required an Advisory Committee meeting.

9. Pediatrics

Ninlaro received orphan designation for this indication and is therefore exempt from the requirements of PREA.

10. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Approval
- Risk Benefit Assessment

Multiple Myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant cured of their disease. The development and approval of proteasome inhibitors and thalidomide analogues has improved the outlook for patients with multiple myeloma with a current median overall survival of approximately 5 years.

The Applicant has submitted the results from a single international, multicenter, randomized, double-blind placebo controlled trial enrolling patients with relapsed disease to either treatment with ixazomib or placebo on a backbone of lenalidomide and dexamethasone. A total of 722 patients were randomized. Progression free survival was 14.7 months (95% CI 12.9, 17.6) in the placebo arm to 20.6 months (95% CI; 17.0, NE) in the ixazomib arm. The stratified hazard ratio was 0.74 (95% CI 0.59, 0.94) with statistically significant p value of 0.012. The most common adverse reactions were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. The major safety issues requiring a warning in the labeling were thrombocytopenia, gastrointestinal toxicity, potential for embryo-fetal toxicity, peripheral neuropathy, peripheral edema, cutaneous reactions, and hepatotoxicity. These side effects can be managed for the majority of patients needing treatment.

Approval of ixazomib may be more convenient for some patients because the triple drug combination of ixazomib, lenalidomide and dexamethasone provides an entirely oral treatment regimen.

The risk:benefit assessment was also discussed in the reviews of Drs. Farrell, DeClaro and Schwarsin. The review team and I recommend approval of this application.

- Recommendation for Post marketing Risk Management Activities
A REMS is not necessary for approval.
- Recommendation for other Post marketing Study Requirements/ Commitments
None.

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/s/

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11/20/2015

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