CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208462Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	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:	
Medical Officer Review	Alexandra Schwarsin, M.D. /Angelo DeClaro, M.D.,
Statistical Review	Yun Wang, Ph.D., /Lei Nie, Ph.D./ Raji Sridhara, Ph.D.
Pharmacology Toxicology Review	Emily Place, Ph.D./Christopher Sheth, Ph.D./John Leighton, Ph.D.
CMC Review/Microbiology	Janice Brown, B.S. M.S./Olen Stephens, Ph.D. and the team
Clinical Pharmacology Review	Vicky Hsu, Ph.D./Jee Eun Lee, Ph.D./Dinko Rekic, Ph.D./Bahru Habtemariam, Pharm.D./Nitin Mehrotra, Ph.D.
OSI	Anthony Orencia, M.D./Susan Thompson, M.D. for Janice Pohlman, M.D., M.P.H., Kassa Ayalew, M.D., M.P.H.
CDTL Review	Angelo DeClaro, M.D.
OSE	Todd Bridges, R.Ph./Kevin Wright/LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Sharon R. Mills, BSN, RN, CCRP/Nisha Patel, Pharm.D./ Amarilys Vega, MD, MPH/ Naomi Redd, Pharm.D./Cynthia LaCivita, Pharm.D./Ebony Ayres, Pharm.D., Yelena Maslov, Pharm. D., Lubna Merchant, MS, Pharm.D.

Signatory Authority Review Template

1. Introduction

On July 10, 2015 Millennium Pharmaceuticals, Inc. (Millennium) submitted a 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.

2. Background

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. However, more therapies with differing adverse event profiles are needed.

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.

3. CMC/Device

No issues were identified that would preclude approval.

From the 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. Inactive ingredients include microcrystalline cellulose, magnesium stearate, and talc. Capsule shells contain gelatin and titanium dioxide. The 4 mg capsule shell contains red and yellow iron oxide, the 3 mg capsule shell contains black iron oxide and the 2.3 mg capsule shell contains red iron oxide. The printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

The product shelf life recommendation is for 36 months when stored below 30^0 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.

All facilities inspections have been completed. According to Office of Process and Facilities, the overall manufacturing inspection recommendation is acceptable.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From 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. Ixazomib will be formulated into capsules of Ninlaro of 2.3, 3, and 4 mg strengths. Ninlaro will be administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle, in combination with lenalidomide and dexamethasone.

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.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified.

The review stated:
Exposure-Response (E-R) Relationships

The results of 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.

6. Microbiology

N/A

7. Clinical/Statistical-Efficacy

From the primary clinical review:

The applicant has provided substantial evidence of effectiveness based on an improvement in progression free survival (PFS)…

The benefit of ixazomib was demonstrated in a randomized, double-blind placebo controlled trial in patients with relapsed multiple myeloma who received 1 to 3 prior lines of therapy. A total of 722 patients were randomized to receive the combination of ixazomib, lenalidomide and dexamethasone or the combination of placebo, lenalidomide and dexamethasone. 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 0.013. The improvement in progressive free survival is abated somewhat with a subsequent non-inferential evaluation, however, there remains a clinically meaningful benefit. Another benefit of ixazomib, compared to currently approved proteasome inhibitors for multiple myeloma, is ixazomib is an oral medication. This may be more convenient for some patients.

The safety of ixazomib was evaluated in the trial mentioned above. The median number of cycles for both arms was 12 (range 1-26). The ixazomib combination arm was not associated with an increase in the rate of deaths within 30 days of the last dose of study drug compared to the placebo combination arm, 3.3% vs 4.7% respectively. A total of 144 patients (40.0%) on the ixazomib combination arm had at least one serious adverse event compared to 161 patients (44.8%) on the placebo combination arm. The serious adverse events that occurred in more than 2% of patients overall are pneumonia (6.5% of all patients) and pyrexia (3.3% of all patients). The treatment emergent adverse events more common on the ixazomib arm, with a greater than 5% difference in incidence between the two arms, were vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea and maculo-papular rash. It is necessary to acknowledge other adverse events increased on the ixazomib combination including peripheral neuropathy (38.9% vs 31.1% SMQ analysis), eye disorders (26.4% vs 15.8% for eye disorder system organ class), and hepatotoxicity (2.2% vs 0% SMQ analysis for drug related severe events only).

The primary efficacy benefit demonstrated was an improvement in progressive free survival on average of 4 to 6 months when ixazomib is added to lenalidomide and dexamethasone. This establishes substantial evidence of efficacy of ixazomib in multiple myeloma when used in combination with lenalidomide and dexamethasone. The risks demonstrated, mainly gastrointestinal disorders, rash, thrombocytopenia and cutaneous reactions are acceptable and do not outweigh the benefit. Ixazomib adds an additional treatment option with a different safety profile to the current armamentarium for the treatment of relapsed multiple myeloma. The recommendation is traditional approval.

From the statistical review:

Study C16010 demonstrated superiority in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) assessments, for RRMM patients. Based on the 1st interim analysis (IA) of PFS, the estimated hazard ratio (HR) for PFS was 0.74 (95% confidence interval: 0.59 – 0.94, p-value = 0.01) for the Ixazomib arm versus Placebo arm; the median PFS was 20.6 months in Ixazomib arm, and was 14.7 months in placebo arm; the estimated HR for overall survival (OS) was 0.9 (95% confidence interval: 0.62 – 1.32) based on 107 deaths, median OS was not reached for either treatment arm. An updated final analysis of PFS and 2nd interim analysis for other efficacy endpoints were submitted during the review of this NDA submission. Based on this updated analysis, the estimated hazard ratio (HR) for PFS was 0.82 (95% confidence interval: 0.67 – 1.0, p-value = 0.0548) for the Ixazomib arm versus Placebo arm; the median PFS was 20.0 months in Ixazomib arm, and was 15.9 months in placebo arm; the estimated HR for overall survival (OS) was 0.87 (95% confidence interval: 0.64 – 1.18) based on 171 deaths, median OS was not reached for either treatment arm.

The submitted data for 1st interim analysis of PFS per IRC support the applicant's claim of efficacy of Ixazomib in combination with lenalidomide and dexamethasone for patients with relapsed and/or refractory multiple myeloma. However, we identified some statistical issues in this submission:

- *Although 1st interim analysis results of PFS per IRC crossed the pre-specified superiority boundary, the final analysis results of PFS were not statistically significant.*
- *There were discordance between PFS per IRC and PFS per investigator. Analysis results for PFS per investigator were not significant for both interim and final analysis.*
- *There were some discrepancies between 1st interim and final PFS data.*

Due to these issues, reliable estimate of the magnitude of treatment effect based on PFS could not be ascertained.

I concur with the findings of the clinical and statistical review teams that the pre-specified analysis based on the agreed upon IRC demonstrated an improvement in median PFS. The statistical group performed a number of additional analyses. In all these additional analyses the median PFS result was longer for the ixazomib (and lenalidomide and dexamethasone) arm compared with the placebo (and lenalidomide and dexamethasone) arm. I concur with both teams that the application should be approved.

8. Safety

The most common adverse reactions (≥ 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.

9. Advisory Committee Meeting

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

10. Pediatrics

This product has orphan designation for this indication.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) did not identify data integrity issues and stated that the study data are considered reliable in support of the requested indication.

Financial Disclosure information was provided and reviewed. No issues were identified.

12. Labeling

All disciplines made recommendations for labeling.

13. 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. However, more therapies with differing adverse event profiles are needed.

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 0.013. 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.

- Recommendation for Post marketing Risk Management Activities
  Routine Pharmacovigilance.

- Recommendation for other Post marketing Study Requirements/ Commitments
  None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/19/2015