APPLICATION NUMBER:

208462Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
Cross-Discipline Team Leader Review

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<td>From</td>
<td>R. Angelo de Claro, M.D.</td>
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<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<td>NDA/BLA #</td>
<td>NDA 208462</td>
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<td>Supplement#</td>
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<tr>
<td>Applicant</td>
<td>Millennium Pharmaceuticals, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>10 July 2015</td>
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<td>PDUFA Goal Date</td>
<td>10 March 2016</td>
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<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Ninlaro / Ixazomib</td>
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<tr>
<td>Dosage forms / Strength</td>
<td>Capsules: 4 mg, 3 mg, 2.3 mg</td>
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<td>Applicant's Proposed Indication</td>
<td>Ninlaro is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.</td>
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<td>Intended Population</td>
<td>see indication</td>
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<td>Recommendation on Regulatory Action</td>
<td>Approval</td>
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<tr>
<td>Recommended Indication</td>
<td>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.</td>
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<td>Clinical Review</td>
<td>Alexandria Schwarsin, M.D. / R. Angelo de Claro, M.D.</td>
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<td>Statistical Review</td>
<td>Yun Wang, Ph.D. / Lei Nie, Ph.D.</td>
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<td>Pharmacology Toxicology Review</td>
<td>Emily Place, Ph.D., M.P.H. / Chris Sheth, Ph.D. / John Leighton, Ph.D.</td>
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<td>CMC Review</td>
<td>Primary Reviewers: Refer to CMC Review Janice Brown, M.S. (Application Technical Lead)</td>
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<td>Clinical Pharmacology Review</td>
<td>Vicky Hsu, Ph.D. (DCPV), Jee Eun Lee, Ph.D. (DPM), Dinko Rekic, Ph.D. (DPM) / Bahru Habtemariam, Pharm.D. (DCPV), Nitin Mehrotra, Ph.D. (DPM)</td>
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<td>OSI/DGCPC</td>
<td>Anthony Orencia, M.D. / Janice Pohlman, M.D., M.P.H.</td>
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<td>OSE/DRISK</td>
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<tr>
<td>OSE/DMEPA</td>
<td>Ebony Ayres, Pharm.D. / Yelena Maslov, Pharm.D.</td>
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<tr>
<td>Patient Labeling Team (DMPP)</td>
<td>Sharon Mills, BSN, RN, CCRP / Barbara Fuller, RN, MSN, CWOCN</td>
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1. **Benefit-Risk Assessment**

The efficacy and safety results from clinical trial C16010 (ClinicalTrials.gov identifier NCT01564537) (Tourmaline-MM1) demonstrate an acceptable benefit-risk profile for Ninlaro, in combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. All review teams recommend approval.

The recommended starting dose of ixazomib is 4 mg orally on days 1, 8, and 15 of a 28 day cycle in combination with lenalidomide 25 mg daily on days 1 through 21 and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28 day treatment cycle.

Clinical trial C16010 was a randomized, double-blind, placebo-controlled trial in patients with multiple myeloma who have received at least one prior therapy. A total of 722 patients were randomized in a 1:1 ratio to receive either the combination of ixazomib, lenalidomide, and dexamethasone (N=360; Ninlaro regimen) or the combination of placebo, lenalidomide and dexamethasone (N=362; placebo regimen) until disease progression or unacceptable toxicity. Randomization was stratified according to number of prior lines of therapy (1 versus 2 or 3), myeloma International Staging System (ISS) (stage I or II versus III), and previous therapy with a proteasome inhibitor (exposed or naïve). Patients who were refractory to lenalidomide or proteasome inhibitors were excluded from the study.

Patients received Ninlaro 4 mg or placebo on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients with renal impairment received a starting dose of lenalidomide according to its prescribing information. Treatment continued until disease progression or unacceptable toxicities.

The primary efficacy endpoint is progression-free survival per IRC using International Myeloma Working Group (IMWG) response criteria. The key secondary efficacy endpoints are overall survival (OS) and overall survival in high risk patients harboring Del17.

Clinical trial C16010 demonstrated superiority in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) assessments. 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. The median OS was not reached for either treatment arm.

The most common adverse reactions (≥ 20%) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain.
**Benefit-Risk Summary and Assessment**

Ixazomib is an oral proteasome inhibitor that reversibly binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome and induces apoptosis in the cell.

Multiple myeloma is a plasma cell neoplasm in which, malignant plasma cells increase and produce a monoclonal immunoglobulin. The clinical features of multiple myeloma include depressed immunity and end-organ damage particularly in the kidneys, bones, and hematopoietic system. Ixazomib is a new molecular entity that provides a new route of administration, oral, compared to currently approved proteasome inhibitors.

Multiple myeloma is an incurable disease, with an average survival of approximately 6 years from the time of diagnosis. Treatment of multiple myeloma is multifaceted comprising of chemotherapeutic agents such as immunomodulating agents, proteasome inhibitors and alkylating agents, stem cell transplantation, and supportive measures such as bisphosphonates to prevent complications of the disease. A typical patient, progresses through several lines of therapy and, over the course of the disease, the periods of inactivity shorten. The patient may become non responsive to treatment and have morbidity and mortality associated with the disease, or the treatment itself. While the median survival of multiple myeloma has been improving, there still remains an unmet medical need and patients need new treatment options.

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 and was 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 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 most common adverse reactions (≥ 20%) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Other adverse events increased on the ixazomib combination including peripheral neuropathy (38.9% vs 31.1% Standardized MedDRA Query [SMQ] analysis), eye disorders (26.4% vs 15.8% for Eye Disorder System Organ Class), and hepatotoxicity (2.2% vs 0% for SMQ “Drug related hepatic disorders - severe events only”).

Reference ID: 3847843
The primary efficacy benefit demonstrated was an improvement in progressive free survival, corresponding to an improvement of median PFS by 5.9 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.

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<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Multiple myeloma is not a curable disease and is associated with morbidity and mortality.</td>
<td>Relapsed multiple myeloma is a progressive and fatal disease.</td>
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<tr>
<td></td>
<td>The typical course of multiple myeloma, as a patient progresses through treatment, is shortened periods of disease inactivity with the disease becoming unresponsive to treatment</td>
<td></td>
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<tr>
<td>Current Treatment Options</td>
<td>Current treatment options are not curative. Current treatments have toxicities that may limit use in certain patients.</td>
<td>Effective therapy for multiple myeloma, with different safety profiles, are necessary to provide options to patients.</td>
</tr>
<tr>
<td>Benefit</td>
<td>In a double-blind, randomized, placebo controlled trial, ixazomib demonstrated an improvement in progression free survival corresponding to a 5.9 month improvement in median PFS when added to lenalidomide and dexamethasone. No improvement in overall survival has been demonstrated.</td>
<td>The addition of ixazomib to lenalidomide and dexamethasone improved progression free survival.</td>
</tr>
<tr>
<td>Risk</td>
<td>Treatment emergent adverse events increased with the addition of ixazomib were vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea, maculopapular rash, and nausea.</td>
<td>The overall safety profile is acceptable to the patient population.</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Serious toxicities are manageable with dose reductions, dose delays and clinical and laboratory monitoring.</td>
<td>The prescribing information will inform providers on adverse reactions and safe administration of ixazomib.</td>
</tr>
</tbody>
</table>
2. Background

On July 10, 2015, Millennium Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) for Ninlaro. The Applicant proposed the following indication: Treatment of patients with multiple myeloma who have received at least one prior therapy.

Ninlaro (ixazomib) is a new molecular entity of the proteasome inhibitor class. Velcade (bortezomib) and Kyprolis (Carfilzomib) are the other approved drugs within the proteasome inhibitor class for the treatment of patients with multiple myeloma. Ninlaro will be the first approved oral proteasome inhibitor. Ninlaro is not approved in any other country.

Multiple myeloma is an incurable disease. Based on SEER data (Surveillance, Epidemiology, and End Results Program), there were an estimated 89,568 people living with multiple myeloma in the United States in 2012. Survival based on SEER 2005-2011 data estimate 46.6% of patients with multiple myeloma surviving 5 years from time of diagnosis.

Treatment of multiple myeloma is multifaceted comprising of chemotherapeutic agents such as immunomodulating agents, proteasome inhibitors, and alkylating agents, hematopoietic stem cell transplantation, and supportive measures such as bisphosphonates to prevent complications of the disease. A typical patient, progresses through several lines of therapy and, over the course of the disease, the periods of inactivity shorten. The patient may become non-responsive to treatment and have morbidity and mortality associated with the disease, or the treatment itself. While the median survival of multiple myeloma has been improving, there still remains an unmet medical need and patients need new treatment options.

The primary basis for the application are the results of clinical trial C16010 (ClinicalTrials.gov identifier NCT01564537) (Tourmaline-MM1), a randomized, double-blind, placebo-controlled trial of 722 patients with previously treated multiple myeloma, which compared the combination of ixazomib, lenalidomide, and dexamethasone to the combination of placebo, lenalidomide, and dexamethasone.

3. Product Quality

Source: CMC Review

CMC Team Recommendation: Approval

- General product quality considerations

Ninlaro (ixazomib) is an antineoplastic agent. Ixazomib citrate, a prodrug, rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib. The chemical name of ixazomib citrate is 1,3,2-dioxaborolane-4,4-diace tic acid, 2-[(1R)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo- and the structural formula is:
The molecular formula for ixazomib citrate is $C_{20}H_{23}BClN_2O_9$ and its molecular weight is 517.12. Ixazomib citrate has one chiral center and is the R-stereoisomer. The solubility of ixazomib citrate in 0.1N HCl (pH 1.2) at 37°C is 0.61 mg/mL (reported as ixazomib). The solubility increases as the pH increases.

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.

A 36 month shelf life is granted for Ixazomib capsules stored at room temperature not to exceed 30°C (86°F). 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. All registration stability studies have been completed through six months at the accelerated storage condition, and will be continued through 48 months at the long-term storage conditions, with 24 months of real time data provided in the submission.

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

- Other notable issues: None

4. **Clinical Microbiology**

Not applicable.

5. **Nonclinical Pharmacology and Toxicology**

*Source: Pharmacology and Toxicology Review*

**Pharmacology Toxicology Team Recommendation:** Approval
• General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

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.

**Mechanism of Action**
Ixazomib is a reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

**Pharmacology**
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.

**Toxicology**
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; AUC$_{0-168}$ = 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.

• Carcinogenicity

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.
Reproductive toxicology

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.

Other notable issues: None

6. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

General clinical pharmacology considerations

Absorption
After oral administration, the median time to achieve peak ixazomib plasma concentrations was one hour. The mean absolute oral bioavailability was 58%, based on population PK analysis. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 to 10.6 mg.

A food effect study conducted in patients with a single 4 mg dose of ixazomib showed that a high-fat meal decreased ixazomib AUC by 28% and C<sub>max</sub> by 69%.

Distribution
Ixazomib is 99% bound to plasma proteins and distributes into red blood cells with a blood-to-plasma ratio of 10. The steady-state volume of distribution is 543 L.

Elimination
Based on a population PK analysis, systemic clearance was approximately 1.9 L/hr with inter-individual variability of 44%. The terminal half-life (t<sub>1/2</sub>) of ixazomib was 9.5 days. Following weekly oral dosing, the accumulation ratio was determined to be 2-fold.

Metabolism
After oral administration of a radiolabeled dose, ixazomib represented 70% of total drug-related material in plasma. Metabolism by multiple CYP enzymes and non-CYP proteins is expected to be the major clearance mechanism for ixazomib. At clinically
relevant ixazomib concentrations, in vitro studies using human cDNA-expressed cytochrome P450 isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib metabolism. At higher than clinical concentrations, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (< 1%).

Excretion
After administration of a single oral dose of $^{14}$C-ixazomib to 5 patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in the feces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

- Drug-drug interactions

In vitro and clinical studies were conducted to characterize the metabolism and drug-drug interaction potential of ixazomib. In vitro studies indicate that both non-CYP and CYP enzymes may contribute to ixazomib metabolism. Clinical DDI studies with strong CYP3A4 inhibitors ketoconazole and clarithromycin did not show clinically meaningful effects on ixazomib systemic exposure. On the other hand, clinical study with the strong CYP3A4 inducer rifampin showed significant decrease in ixazomib exposure (AUC ↓74%, CMAX ↓54%).

- Pathway of elimination

Refer to General Clinical Pharmacology considerations.

- Intrinsic factors potentially affecting elimination, Demographic interactions, and Special populations

There was no clinically meaningful effect of age (range 23-91 years), sex, body surface area (range 1.2-2.7 m2), or race on the clearance of ixazomib based on population PK analysis.

Hepatic and renal impairment studies showed that ixazomib systemic exposure was increased by 13-42% in patients with moderate or severe hepatic impairment and those with severe renal impairment or end stage renal disease requiring dialysis compared to patients with normal hepatic and renal functions.

- Thorough QT study or other QT assessment

Ninlaro (ixazomib) did not prolong the QTc interval at clinically relevant exposures based on pharmacokinetic-pharmacodynamic analysis of data from 245 patients.

- Other notable issues: None
7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews

**Statistical Team Recommendation:** Approval  
**Clinical Team Recommendation:** Approval

Study C16010 is a randomized, double-blinded, multi-center study of Ixazomib plus lenalidomide and dexamethasone versus Placebo plus lenalidomide and dexamethasone in subjects with RRMM. The primary efficacy endpoint is progression-free survival per IRC using International Myeloma Working Group (IMWG) response criteria. The key secondary efficacy endpoints are overall survival (OS) and overall survival in high risk patients harboring Del17.

Approximately 703 patients were planned to be randomized 1:1 to the 2 treatment arms via an interactive voice response system (IVRS). Randomization was stratified by three factors: (a) 1 versus 2 or 3 prior therapies; (b) Proteasome inhibitor [PI]-exposed versus PI-naïve; and (c) International Staging System [ISS] stage 1 or 2 versus stage 3.

The original protocol for Study C16010 was dated 21 February 2012, and the latest version was Amendment 3 dated 08 July 2014.

**Statistical Assumptions**

In the original protocol, there was one and only analysis for PFS, which was planned at 234 PFS events. With amendment 3 dated 08 July 2014, timing for PFS analysis was revised, one interim efficacy analysis of PFS was added at ~262 PFS events, and the final PFS analysis was changed to when ~365 PFS events occur. Lan-DeMets spending function with O’Brien Fleming boundary was used to determine superiority boundaries for both interim and final PFS analyses.

In the original protocol, the sample size was calculated based on maintaining 80% power to test the first key secondary endpoint OS. There were two interim and one final analyses planned for OS at ~118, ~322, and ~482 deaths respectively. Assuming a hazard ratio of 0.77 (median survival of 30 months in placebo arm versus 39 months in Ixazomib arm), a total of approximately 703 patients would be needed to test OS with 80% power and 2-sided type I error rate of 5%, assuming an average enrollment rate of approximately 13 patients/month for the first 6 months, 30 patients/month thereafter, and approximately 10% dropout rate. With 234 PFS events, it will have 90% power to detect a hazard ratio of 0.66 (median PFS of 11 months for placebo versus 16.8 months for Ixazomib) with a 2-sided alpha level of 0.05.

In protocol amendment 3, the sample size was the same but the assumption for sample size justification was revised according to the latest research findings. The assumed median PFS was revised to 15 months for the placebo arm and 20.6 months for the Ixazomib arm, the assumed HR was revised to 0.728, and the power for PFS analysis was reduced to 85%. The power analysis for OS in amendment 3 was similar to that in original protocol, except that
there would be 3 interim and 1 final analyses of OS at ~154, ~222, ~322, and ~486 deaths respectively.

**Efficacy Results**

A total of 722 patients were enrolled between 28 August 2012 and 27 May 2014 from 147 study centers in 26 countries. The data cut-off date was 30 October 2014 for the 1st interim analysis of PFS per IRC (286 PFS events), and was 12 July 2015 for the 2nd interim analysis of PFS per IRC (372 PFS events).

By region, 483 patients (67%) were enrolled from 91 sites in Europe, 143 patients (20%) were enrolled from 35 sites in the Asia-Pacific (APAC) region, and 96 patients (13%) were enrolled from 21 sites in North America (NA). The baseline demographics and disease characteristics were balanced and comparable between the study regimens.

Study C16010 demonstrated superiority in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) assessments. Based on the 1st interim analysis (LA) 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. Kaplan-Meier plot is presented in Figure 1. The estimated HR for overall survival (OS) was 0.9 (95% confidence interval: 0.62 – 1.32) based on 107 deaths. The median OS was not reached for either treatment arm. Response rate information is presented in Table 1.

**Figure 1** Kaplan-Meier Plot of PFS Analysis at a Median Follow-up of 15 Months
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. The median OS was not reached for either treatment arm.

**Conclusions on the Substantial Evidence of Effectiveness:** The efficacy results of clinical trial C16010 provide substantial evidence of effectiveness. C16010 demonstrated a statistically significant and clinically meaningful improvement in the primary efficacy endpoint of progression-free survival (PFS). Improvement in PFS based on a single, adequate, and well-controlled trial has been used in previous FDA approvals for the treatment of patients with multiple myeloma.

## 8. Safety

*Source: Clinical Review*

**Clinical Team Recommendation: Approval**

The overall safety population consisted of 990 patients across 15 clinical trials. The duration of exposure for the overall safety population is summarized below.
Table 2 Safety Database for Ixazomib

<table>
<thead>
<tr>
<th>Clinical Trial Groups</th>
<th>Ixazomib (n= 990)</th>
<th>Active Control with placebo (n=360)</th>
<th>Placebo (n=0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Volunteers</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Controlled trials conducted for this indication¹</td>
<td>360</td>
<td>360</td>
<td>0</td>
</tr>
<tr>
<td>All other than controlled trials conducted for this indication</td>
<td>630²</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Controlled trials conducted for other indications</td>
<td>N/A³</td>
<td>N/A³</td>
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</tbody>
</table>

1. to be used in product’s labeling
2. All patients who received open-label treatment with ixazomib (either as a single agent or in combination with other chemotherapeutic regimens) for all indications included in the safety database (C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16011, C16013, C16015, C16017, C16018, C16020, and TB-MC010034).
3. Controlled trials for other indications are ongoing and remain blinded. Therefore, exposure by arm is not available for studies, C16014, C16019 and the C16010 China continuation.

Table 3 Duration of Exposure for Overall Safety Database

<table>
<thead>
<tr>
<th>Number of patients exposed to the study drug = 990</th>
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<tr>
<td>&gt;=6 months</td>
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<tr>
<td>N=483</td>
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</table>

The primary safety population used in the safety analysis and labeling was 720 patients treated with either ixazomib or placebo combined with lenalidomide and dexamethasone. The median number of cycles for the 360 patients on the ixazomib, lenalidomide and dexamethasone arm was 13 (range 1-26).

For the safety population the principle safety findings through 30 days after the last dose of study drug are:

- The addition of ixazomib to lenalidomide and dexamethasone did not result an increase in deaths with 3.3% of patients dying within 30 days of last dose on the ixazomib + LenDex arm compared to 4.7% on the placebo + LenDex arm.
- The more common serious adverse events overall were pneumonia and pyrexia. Serious adverse reactions reported in \( \geq 2\% \) of patients and that were common on the ixazomib arm include thrombocytopenia (2%) and diarrhea (2%).
- Ixazomib was associated with an approximately 1.5% increase risk of discontinuation.
from the trial or discontinuation of ixazomib due to a treatment emergent adverse event. There was an 11% increase in delay, holding, reduction, or discontinuation of ixazomib compared to placebo as a result of an adverse event.

- Treatment-emergent adverse events associated with a greater than 5% increase in incidence on the ixazomib + LenDex arm are vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea, rash and nausea.

- The laboratory tests were the incidence of grade 3 and 4 abnormalities was greater than 5% on the ixazomib + LenDex arm are thrombocytopenia, lymphopenia, and leukopenia.

- No clear dose-response and exposure-response for QTc was observed.

- The proportion of patients experiencing peripheral neuropathy was increased by 7.8% in the ixazomib, lenalidomide and dexamethasone arm.

- TEAE in the system order class of eye disorders was increased to 26.4% in the ixazomib + lenalidomide and dexamethasone arm compared to 15.8% in the placebo + lenalidomide and dexamethasone arm. The majority of these were conjunctivitis, dry eyes and vision blurred. There was an approximately 2.2% increase risk of visual disturbance with ixazomib.

- A potential safety signal is present for drug related severe hepatic disorders, which may be a class effect for proteasome inhibitors.

9. Advisory Committee Meeting

This New Molecular Entity (NME) application was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the indication to be approved.

10. Pediatrics

Ninlaro is exempt from pediatric study requirements described in 21 CFR 314.55. FDA granted Orphan Drug Designation for Ninlaro for the treatment of multiple myeloma on 18 February 2011.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.

- Exclusivity or Patent Issues of Concern: No issues.

- Financial Disclosures: In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirement and certification for clinical trial C16010.

- Other GCP Issues: None
Office of Scientific Investigation (OSI) Audits: FDA Office of Scientific Investigations performed inspections of the following clinical sites: John Theurer Cancer Center Hackensack University Medical Center (Hackensack, NJ), St. István and St. Laszlo Hospital (Budapest, Hungary), and Samodzielny Publiczny Szpital Kliniczny Nr 1 (Katowice, Poland). OSI also inspected the Applicant on October 19-23, 2015. OSI concluded that the study data are considered reliable in support of the requested indication.

Other outstanding regulatory issues: None

12. Labeling

The following are recommended major changes to the ixazomib prescribing information:

1. Indications and Usage
   - Modified the indication that that ixazomib is indicated in combination with lenalidomide and dexamethasone in the treatment of multiple myeloma in patients with at least one prior line of therapy

2. Dosage and Administration
   - Recommended the addition of dose modification guidelines for neutropenia and other non-hematologic toxicities

5. Warnings and Precautions
   a. Recommended additional warnings and precautions of peripheral neuropathy, peripheral edema, cutaneous reactions, and hepatotoxicity.

6. Adverse Reactions
   - A subsection to address ocular toxicities was recommended.

14. Clinical Studies
   - Recommended the applicant add the updated progression free survival results to the prescribing information.

Labeling Consults

- Proprietary name: On 25 August 2015, OSE/DMEPA concluded that the proposed proprietary name, Ninlaro, was found conditionally acceptable.

- Patient labeling/Medication guide: DMPP and OPDP participated in the labeling discussions, and reviewed the patient package insert (PPI).

- Carton and immediate container labels: DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.
13. **Postmarketing Recommendations**

- Risk Evaluation and Management Strategies (REMS): The review teams did not identify a need for REMS to ensure the safe use of ixazomib.

- Postmarketing Requirements (PMRs) and Commitments (PMCs): No PMRs or PMCs were requested.

14. **Recommended Comments to the Applicant**

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
11/17/2015

Reference ID: 3847843