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RESEARCH**

APPLICATION NUMBER:

208462Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management Review

Application Type NDA

Application Number 208462

Submission # 0000 and 0008

OSE RCM # 2015-1583

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Review Completion Date November 16, 2015

Established Name Ixazomib

(Proposed) Trade Name Ninlaro

Applicant Millennium Pharmaceuticals

Therapeutic Class Proteasome inhibitor

Formulation(s) (b) (4) gelatin capsule 2.3 mg, 3 mg, 4 mg

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

Proposed Indication(s) Treatment of patients with multiple myeloma who have received at least one prior therapy

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ixazomib is necessary to ensure the benefits of this product outweigh its risks. Millennium Pharmaceuticals submitted a New Drug Application for ixazomib (NDA 208462) for the treatment of patients with multiple myeloma who have received at least one prior therapy. The applicant did not submit a proposed REMS or risk management plan with this application.

Ixazomib, is an oral small molecule inhibitor of the 20S proteasome. Proteasome inhibitors interfere with tumor survival pathways, block proliferation of multiple myeloma cells, inhibit angiogenesis and prevents bone loss associated with activation of osteoclasts and osteoblasts.

Multiple myeloma is considered an incurable disease and, in spite of the availability of several drug therapies, most patients will eventually relapse and require additional treatment. The available treatments have serious dose- and treatment duration-limiting adverse reactions which often result in suboptimal therapy.¹ In addition, most of the available therapies, including other approved proteasome inhibitors, are administered parenterally requiring frequent visits to the hospital or clinic. Therefore, there is a medical need for effective multiple myeloma therapies with increased tolerability and ease of administration.

The pivotal trial (study C16010) supporting this application consisted of a double-blind, placebo-controlled, multicenter study evaluating the combination of ixazomib with lenalidomide and dexamethasone in 722 patients. The trial showed that the ixazomib treatment group had a statistically significant 35% improvement in median progression free survival (PFS) (HR=0.742; p=0.012) over the placebo regimen.

The safety profile observed for ixazomib is comparable to that observed with other drugs in the class. Important safety concerns include thrombocytopenia, gastrointestinal toxicity, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity and embryo-fetal toxicity. Based on the available data, risk mitigation measures beyond professional labeling are not warranted for ixazomib. The benefit-risk profile of ixazomib is acceptable and a REMS is not necessary to ensure the benefits outweigh the risks of ixazomib when used in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. Healthcare providers who treat multiple myeloma are typically highly specialized and expected to be familiar with the risk associated with the use of Ninlaro and understand the importance of frequent patient monitoring.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ixazomib is necessary to ensure the benefits of this product outweigh its risks. Millennium Pharmaceuticals submitted a New Drug Application for ixazomib (NDA 208462) for the treatment of patients with multiple myeloma who have received at least one prior therapy. The applicant did not submit a proposed REMS or risk management plan with this application. On February 18, 2011, Millennium received orphan designation for ixazomib for the treatment of multiple myeloma. This application was classified as a Priority review on September 8, 2015.

2 Background

2.1 PRODUCT INFORMATION¹

Millennium Pharmaceuticals is seeking approval for ixazomib, a New Molecular Entity (NME, 505 (b) (1)), as a treatment for patients with multiple myeloma who have received at least 1 prior therapy. The pivotal study was conducted under IND 104,482. Ixazomib, is an oral small molecule inhibitor of the 20S proteasome that is administered as ixazomib citrate, a prodrug of ixazomib. The ubiquitin-proteasome system is the major regulator of protein homeostasis. The 26S proteasome has a catalytic proteolytic core (20S) and 2 regulatory subunits (19S). Inhibition of the 20S proteasome pathway demonstrated to be useful in the treatment of multiple myeloma. Proteasome inhibition interferes with tumor survival pathways (e.g., anti-apoptosis and nuclear factor-driven proliferation, inflammation and survival), blocks proliferation of multiple myeloma cells, inhibits angiogenesis and prevents bone loss associated with activation of osteoclasts and osteoblasts. Ixazomib has in vitro cytotoxicity against myeloma cells from patients who had relapsed after multiple drugs (e.g., bortezomib (Velcade[®]), lenalidomide (Revlimid[®]), or dexamethasone). In addition, ixazomib in combination with lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines.

The proposed commercial formulation is a (b) (4) gelatin capsule provided in product strengths of 2.3 mg, 3 mg, and 4 mg. The recommended starting dose of ixazomib is 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle.² An alternating dose modification approach is recommended for ixazomib and lenalidomide for (b) (4) thrombocytopenia and rash.² (b) (4)

On February 18, 2011, Millennium received orphan designation for ixazomib for the treatment of multiple myeloma. This application was classified as a Priority review on September 8, 2015. At

¹ Ixazomib Clinical Overview, received by FDA on August 7, 2015.

² Ixazomib draft product label, last modified 10/19/2015.

the time of this review, ixazomib has not been licensed by any other regulatory agency. If approved, ixazomib will be used primarily in the outpatient setting.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for ixazomib [NDA 208462] relevant to this review:

- **02/18/2011:** The Agency granted the ixazomib orphan designation.
- **07/10/2015:** The Agency received NDA 208462 submission for the treatment of patients with multiple myeloma who have received at least one prior therapy
- **08/18/2015:** FDA (OSE Division of Pharmacovigilance) sent Millennium Pharmaceuticals an information request with the following comment:

“FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **ixazomib** following market approval. Guidance for pharmacovigilance planning is included in the *FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005), and the *FDA Guidance for Industry on E2E Pharmacovigilance Planning* (2005); guidance documents are attached. If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.”
- **08/24/2015:** Millennium Pharmaceuticals submits to FDA their proposed risk management plan for ixazomib. The proposed plan includes routine and enhanced pharmacovigilance (i.e., event specific follow-up forms will be used to capture relevant follow-up information for spontaneous reports of thrombocytopenia and severe dermal events) and the collection of additional safety information from the 4 ongoing phase 3 studies (C16010, C16014, C16019, and C16021).
- **08/25/2015:** The proposed proprietary name, Ninlaro, was granted conditional approval.
- **09/08/2015:** The application was classified as a Priority review.
- **10/13/2015:** Mid-cycle teleconference with the sponsor. The application is on track for approval.

3 Medical Condition(s) and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION³

Multiple myeloma is a malignant proliferation of plasma cells derived from a single clone which results in multiple organ dysfunctions and symptoms, including bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity. Multiple myeloma increases in incidence with age; median age at diagnosis is 70 years; it is uncommon under age 40. Multiple myeloma is more common among males and blacks, accounting for about 1.3% of all malignancies in whites, 2% in blacks. In 2014, there were about 24,050 new cases of myeloma and about 11,090 deaths from the disease in the United States. Rosenberg et al projected a substantial increase in the incidence and burden of multiple myeloma in the US.⁴ See Figure 1 below.

The projections reported by Rosenberg et al are consistent with estimates by the American Cancer Society included by the sponsor in this submission.¹

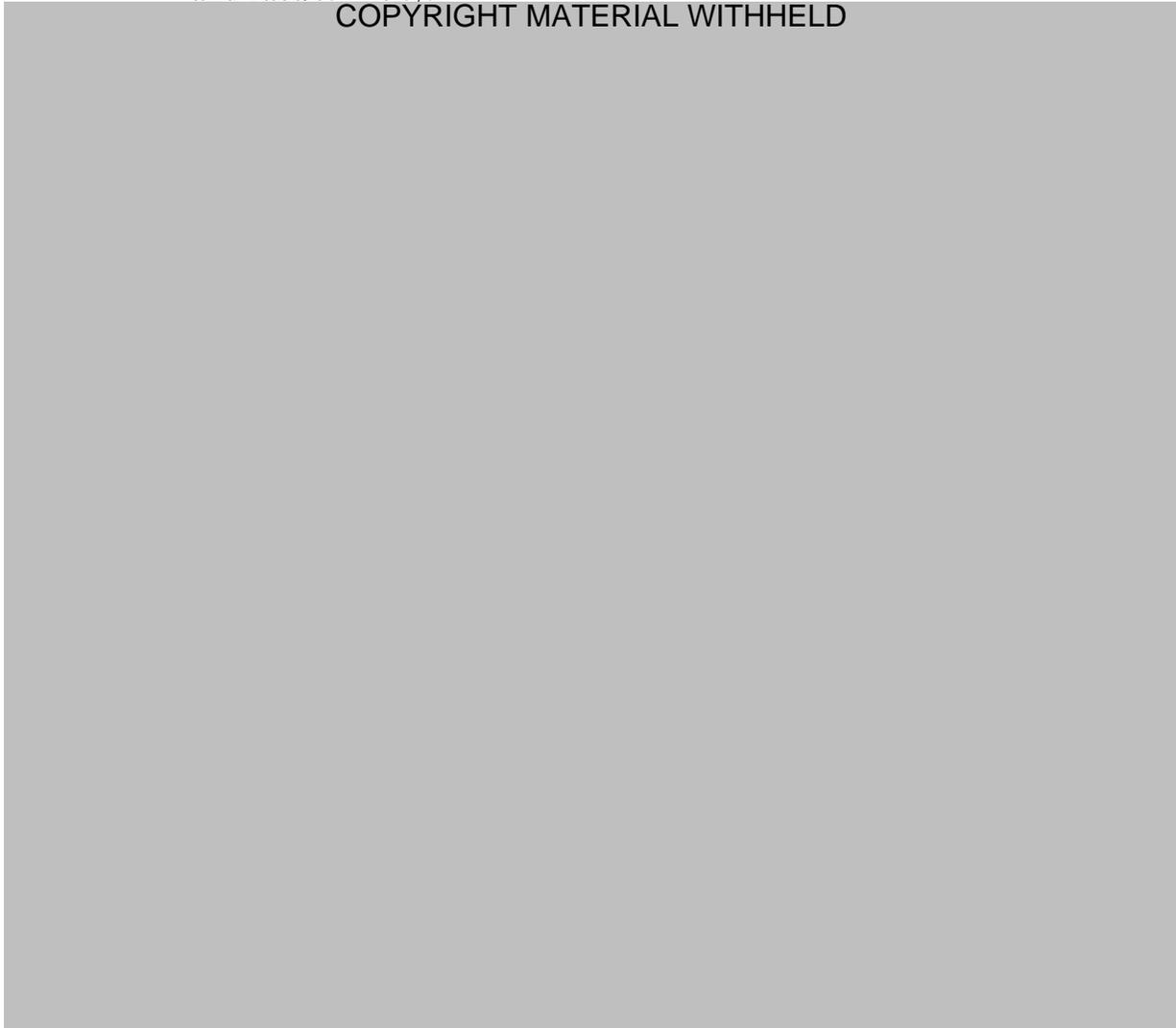
Most patients experience multiple relapses requiring several lines of treatment for their disease.¹ Despite the significant improvement in treatment options, the effect of currently available therapies, including combination regimens, is often transient.¹ Patients with high-risk cytogenetic abnormalities (e.g., translocation of chromosomes 4 and 14 [t(4;14)], translocation of chromosomes 14 and 16 [t(14;16)], and deletion of chromosome 17p13 [del(17)],) represent approximately 20% of patients with multiple myeloma and tend to have shorter survival due to early relapses and the development of resistance to multiple therapies.¹

³ Munshi NC, Longo DL, Anderson KC. Munshi N.C., Longo D.L., Anderson K.C. Munshi, Nikhil C., et al. Plasma Cell Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J Eds. Dennis Kasper, et al.eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79732153>. Accessed October 16, 2015.

⁴ Rosenberg PS1, Barker KA1, Anderson WF1. Future distribution of multiple myeloma in the United States by sex, age, and race/ethnicity. *Blood*. 2015 Jan 8;125(2):410-2. doi: 10.1182/blood-2014-10-609461.

Figure 1. Observed and projected burden of multiple myeloma in the US by sex and race/ethnicity.⁴

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Source: Rosenberg et al⁴

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment modalities used for multiple myeloma include chemotherapy and other drugs, bisphosphonates, radiation, surgery, biologic therapy (interferon), stem cell transplants, and plasmapheresis.^{5,6}

⁵ American Cancer Society: <http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-treating-general-info>, accessed on October 19, 2015.

⁶ Alexandria Schwarsin, MD, clinical review, dated November 12, 2015.

Drugs can be used as monotherapy but most often are used in combination depending on the severity of the disease (e.g., presence of high-risk cytogenetic abnormalities), stage (e.g., newly diagnosed, relapsing), age, renal function, and previous therapies. FDA approved drug therapies include corticosteroids, cytotoxic agents (melphalan), cyclophosphamide (Cytosan[®]), carmustine, doxorubicin hydrochloride liposome); proteasome inhibitors (bortezomib (Velcade[®]), carfilzomib (Kyprolis[®]); immunomodulators (thalidomide (Thalomid[®]), lenalidomide (Revlimid[®]), pomalidomide (Pomalyst[®])); and histone deacetylase (HDAC) inhibitors (panobinostat (Farydak[®])).⁵ Table 1 below shows a side-by-side comparison of FDA approved proteasome inhibitors and ixazomib.

Multiple myeloma is considered an incurable disease and, in spite of the availability of several drug therapies, most patients will eventually relapse and require additional treatment. The available treatments have serious dose- and treatment duration-limiting adverse reactions which often result in suboptimal therapy.¹ In addition, most available therapies are administered parenterally requiring frequent visits to the hospital or clinic. Therefore, there is a medical need for effective multiple myeloma therapies with increased tolerability and ease of administration.

Table 1: FDA Approved Proteasome Inhibitors versus Ixazomib (*application undergoing FDA review*)

| Product Name | Carfilzomib (Kyprolis [®]) | Bortezomib (Velcade [®]) | Ixazomib ⁷ (Ninlaro) |
|-------------------------|---|--|---|
| Year of Approval | July 20, 2012 | May 13, 2003 | FDA Review ongoing |
| Indication | Monotherapy - treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Combination with lenalidomide and dexamethasone - indicated for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy. Approval is based on response rate. Clinical benefit, such as | Treatment of patients with multiple myeloma | Treatment of patients with multiple myeloma who have received at least one prior therapy. |

⁷ Ninlaro draft product label, accessed November 9, 2015.

| Product Name | Carfilzomib (Kyprolis®) | Bortezomib (Velcade®) | Ixazomib ⁷ (Ninlaro) |
|--|---|---|--|
| | improvement in survival or symptoms, has not been verified. | | |
| Dosing/ Administration | 20 mg/m ² ; IV | 1.3 mg/m ² ; IV or SC | 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle |
| Important Safety and Tolerability Issues | <ul style="list-style-type: none"> • Hepatic Toxicity and Hepatic Failure • Embryo-fetal Toxicity • Thrombocytopenia • Cardiac toxicities • Pulmonary Toxicity • Tumor Lysis Syndrome • Posterior reversible encephalopathy syndrome • Hypertension including hypertensive crisis • Pulmonary Hypertension • Dyspnea • Venous Thrombosis • Infusion Reactions • Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome • Acute Renal Failure | <ul style="list-style-type: none"> • Hepatic Toxicity • Embryo-fetal Risk • Thrombocytopenia or Neutropenia • Gastrointestinal Toxicity • Peripheral Neuropathy • Cardiac Toxicity • Pulmonary Toxicity • Tumor Lysis Syndrome • Posterior Reversible Encephalopathy Syndrome • Hypotension | <ul style="list-style-type: none"> • Hepatotoxicity • Embryo Fetal Toxicity • Thrombocytopenia • Gastrointestinal Toxicity • Peripheral Neuropathy • Peripheral Edema • Cutaneous COP |
| Risk Management Approaches/ Boxed Warning | <ul style="list-style-type: none"> • No REMS • Warnings and Precautions • Patient Counseling Information and FDA-approved patient labeling | <ul style="list-style-type: none"> • No REMS • Warnings and Precautions • Patient Counseling Information and FDA-approved patient labeling | <ul style="list-style-type: none"> • No REMS • Warnings and Precautions • Patient Counseling Information and FDA-approved patient labeling |

4 Benefit Assessment⁶

The pivotal trial (study C16010) supporting this application consisted of a double-blind, placebo-controlled, multicenter study which evaluated the combination of ixazomib with lenalidomide and dexamethasone in 722 patients (ixazomib group=360, placebo group=362) with relapsed and/or refractory multiple myeloma who have received at least 1 prior therapy. Study C16010 primary endpoint was progression free survival (PFS). The ixazomib treatment group had a statistically significant 35% improvement in median PFS (HR=0.742; p=0.012) over the placebo regimen. Results show an improvement in progression free survival in the range of 5.9 months

based on the primary analysis. The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on an improvement in progression free survival.

5 Risk Assessment

The integrated analysis of safety includes 990 patients treated with oral ixazomib either as a single agent or in combination with other regimens; the majority of these 990 patients had multiple myeloma (791 patients; 80%).⁸

(b) (4)
Important treatment emergent adverse events identified in the pivotal trial included:

- Thrombocytopenia (20% vs 10%)
- Rash (9% vs 3%)
- Peripheral edema (25% vs 18%)
- Constipation (33% vs 25%)
- Vomiting (21% vs 10%)
- Diarrhea (41% vs 26%)
- Nausea (26% vs 21%)

The safety profile observed for ixazomib is comparable to that observed with carfilzomib and bortezomib (see Table 1 above). The sponsor initially proposed inclusion of embryo fetal toxicity, thrombocytopenia and gastrointestinal toxicity in the Warning and Precautions section of the label. However, the FDA safety review also identified the following risks to be included in the Warnings and Precaution section of the label: hepatotoxicity, peripheral edema, neuropathy, cutaneous reactions. (b) (4)

- Embryo-fetal Toxicity: ² Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures (b) (4) those observed in patients receiving the recommended dose.
- Thrombocytopenia: ⁷ (b) (4) thrombocytopenia (b) (4) reported with ixazomib with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the (b) (4) regimen and 1% of patients in the placebo regimen had a platelet count $\leq 10,000/\text{mm}^3$ during treatment. Less than 1% of patients in both regimens had a platelet count $\leq 5000/\text{mm}^3$ during treatment. (b) (4) discontinuation (b) (4)

⁸ Ixazomib, Integrated Summary of Safety, Table 18.1.1.2.1A, received by FDA on August 7, 2015.

one or more of the three drugs in < 1% of patients in the ixazomib regimen and 2% of patients in the placebo regimen.

- Gastrointestinal Toxicities: ⁷ Nausea, vomiting, and diarrhea (b) (4) reported with ixazomib, occasionally requiring use of antiemetic and antidiarrheal medications, and supportive care. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the ixazomib regimen and < 1% of patients in the placebo regimen.
- Peripheral Neuropathy: ⁷ The majority of peripheral neuropathy (b) (4) were Grade 1 (18% in the Ninlaro regimen and 14% in placebo regimen) and Grade 2 (8% in the Ninlaro regimen and 5% in placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions.
- Peripheral Edema: ⁷ Peripheral edema was reported in 25% and 18% of patients in the Ninlaro and placebo regimens, respectively. The majority of peripheral edema events were Grade 1 (16% in the Ninlaro regimen and 13% in placebo regimen) and Grade 2 (7% in the Ninlaro regimen and 4% in placebo regimen).
- Cutaneous Reactions: ⁷ Rash was reported in 19% of patients in the Ninlaro regimen and 11% of patients in the placebo regimen.⁷ The majority of the rash events were Grade 1 (10% in the Ninlaro regimen and 7% in the placebo regimen) or Grade 2 (6% in the Ninlaro regimen and 3% in placebo regimen). Grade 3 rash was reported in 3% of patients in the Ninlaro regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash.

Hepatotoxicity: ⁷ Events of liver impairment have been reported (6% in the Ninlaro regimen and 5% in the placebo regimen).

6 Discussion of Need for a REMS

Multiple myeloma is a serious life-threatening disease which is typically managed by specialized prescribers. Ixazomib will most likely be prescribed by specialists (oncologists) with extensive experience managing cancer patients and the serious adverse reactions associated with the use of Ninlaro (i.e., thrombocytopenia, gastrointestinal adverse effects, (b) (4) hepatic toxicity, (b) (4) and peripheral edema). Ixazomib will be self-administered by the patients and their care providers in the outpatient clinical setting.

The serious risks associated with the use of ixazomib can be managed with labeling (e.g., instructions for dose reductions, dose delays and clinical and laboratory monitoring recommendations) and do not require a boxed warning or the implementation of a REMS to

maintain a favorable benefit-risk balance. Similar risks reported for the other two drugs in the class (bortezomib and carfilzomib) are managed through labeling. The decision to not require a REMS for ixazomib is consistent with these prior actions.

Females and males of reproductive potential

(b) (4)

The safe use of ixazomib will require that prescribers monitor platelet counts closely and adjust the dose accordingly. Similarly, prescribers should modify the dose in case the patient develops severe gastrointestinal symptoms (Grade 3-4).

Millennium Pharmaceuticals proposed risk management plan consists of labeling (no boxed warning), routine and enhanced pharmacovigilance (i.e., event specific follow-up forms will be used to capture relevant follow-up information for spontaneous reports of thrombocytopenia and severe dermal events) and the collection of additional safety information from the 4 ongoing phase 3 studies (C16010, C16014, C16019, and C16021).

7 Conclusion & Recommendations

Based on the available data, DHP and DRISK agree that risk mitigation measures beyond professional labeling are not warranted for ixazomib. The benefit-risk profile of ixazomib is acceptable and a REMS is not necessary to ensure the benefits outweigh the risks of ixazomib when used in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. Healthcare providers who treat multiple myeloma are typically highly specialized and expected to be familiar with the risk associated with the use of Ninlaro and understand the importance of frequent patient monitoring.

If new safety information becomes available that changes the benefit-risk profile, please send a consult to DRISK to reevaluate this recommendation.

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/s/

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11/16/2015

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