CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761035Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	November 2, 2015
Reviewer(s):	Mona Patel, Pharm.D. Division of Risk Management
Acting Team Leader:	Naomi Redd, Pharm.D. Division of Risk Management
Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Subject:	Review to determine if a REMS is necessary
Established Drug Name(s):	elotuzumab
Proprietary Drug Name:	Empliciti
Therapeutic Class: antibody	humanized immunoglobulin G1 (IgG1) monoclonal (mAb)
Dosing Regimen:	10 mg/kg administered intravenously (IV) every week for the first two cycles and every 2 weeks thereafter when administered with lenalidomide and low-dose dexamethasone
Proposed Indication (s):	the treatment of multiple myeloma in patients who have received one or more prior therapies
Division:	Division of Hematology Products (DHP)
Application Type/Number:	BLA 761035
Applicant/sponsor:	Bristol Myers Squibb Company
OSE RCM #:	2015-1372 2015-1375

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Empliciti (elotuzumab). The applicant, Bristol Myers Squibb (BMS), submitted a Biologics License Application (BLA) 761035 with the proposed indication for the treatment of multiple myeloma in patients who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4) .

BMS included a Risk Management Plan (RMP) with their application. The RMP identified the risk of infusion related reactions associated with elotuzumab administration. Bristol Myers Squibb plan is to address the risk with Patient Prescribing Information. BMSdid not submit a REMS.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- BMS Clinical Modules (sections 2.5, 2.7.3 and 2.7.4)
- Risk Management Plan Module (section 1.16)
- Midcycle Slides, September 15, 2015
- Empliciti (elotuzumab) draft label, October 15, 2015

3 REGULATORY HISTORY

The review timeline for this application is priority. Listed below are the pertinent regulatory history milestones for this NDA:

- July 11, 2006 – IND 100043 submitted for elotuzumab
- May 12, 2014 – Breakthrough Therapy designation
- March 9, 2015 – Type B Pre-BLA Meeting
- May 27, 2015 – Part 1 of Rolling BLA
- June 27, 2015 – Part 2 of Rolling BLA
- August 3, 2015 – Applicant Orientation Presentation
- September 15, 2015 – Midcycle meeting
- September 28, 2015 – Midcycle teleconference with the sponsor
- October 29, 2015 – Late Cycle Meeting
- February 29, 2015 – PDUFA (Action) date

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT[1]

Multiple myeloma is the second most common (10-13%) hematological malignancy in the US after Non-Hodgkin's lymphoma with a 5-year prevalence estimated as 46,009 patients, an incidence of 19,626 per year and 11,978 deaths annually. According to the American

[1] Clinical Overview (section 2.5), Elotuzumab

Cancer Society, in 2015, it is estimated that ~ 26, 850 new cases of multiple myeloma would occur in the United States, and an estimated 11,240 people would die from multiple myeloma during that year.[2] Multiple myeloma is one of the few cancers with the highest projected increase in incidence in the next 20 years (57% increase by 2030) primarily due to the aging population. Multiple myeloma is more common in men than women and among individuals of African American descent.[3] The average age at diagnosis is 70 years. Multiple myeloma is responsible for 10-13% of deaths from hematological cancer and about 1% of all deaths from cancer. According to the National Cancer Institute's SEER database, between 2005-2011, the 5-year survival rate for patients diagnosed with multiple myeloma was close to 47% with most patients surviving only 3 years after their initial remission from first line multiple myeloma therapy.[3,4]

Approved first-line treatment options in the US for multiple myeloma include lenalidomide, bortezomib and thalidomide. Second-line treatment options approved for patients include lenalidomide, bortezomib, and doxorubicin while for third-line treatment options, bortezomib, carfilzomib, pomalidomide, and panobinostat are approved for multiple myeloma. Despite the available chemotherapy options, relapse is inevitable. Since there is no cure, most patients will survive only 3 years after their initial remission from first line multiple myeloma therapy, and it will typically reappear more aggressively after each relapse. There is an existing need for more effective therapies to treat multiple myeloma. This is evidenced by a median progressive free survival (PFS) of 11 months for second-line therapy and a median PFS of 3-4 months for third-line therapy.

Elotuzumab – Elotuzumab is a first-in-class, humanized immunoglobulin G1 monoclonal antibody targeting Signaling Lymphocyte Activation Molecule Family 7. According to the applicant's submission, elotuzumab binding to SLAMF7 directly activates natural killer cells and when bound to myeloma cells via SLAMF7 further activates NK cells via Fc receptors. The indication was revised by the review division for elotuzumab to be used in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

The recommended dose of elotuzumab is 10 mg/kg administered intravenously (IV) every week for the first two cycles and every 2 weeks thereafter when administered with lenalidomide and low-dose dexamethasone every 28 days until disease progression, unacceptable toxicity (b) (4) The key withdrawal criteria were the following: withdrawal of informed consent, pregnancy, progressive disease, grade 4 infusion reaction or any adverse event, laboratory abnormality or inter-current illness which in the opinion of the investigator indicated that continued participation in the study was not in the best interest of the subject.

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[2] http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics accessed 8/26/2015

[3] http://seer.cancer.gov/statfacts/html/mulmy.html accessed 9/8/15

[4] Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia (2009) 23, 2147–2152

4.2 CLINICAL DEVELOPMENT PROGRAM

Efficacy data for elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) for the treatment of patients with multiple myeloma who have received one to three prior therapies was primarily derived from the Phase 3 study, Study CA204004. The development program also included the following completed studies:

An additional 2 studies were ongoing: Study CA204006 with lenalidomide/ dexamethasone in newly diagnosed multiple myeloma and CA204112 with lenalidomide/dexamethasone safety study of 60 minute infusion in relapsed/refractory and newly diagnosed multiple myeloma. Study HuLuc63-1703 is a supportive study for E-LD.

4.2.1 Efficacy

At the time of this writing, the FDA clinical reviewer, Dr. Nicole Gormley, was still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies submitted to support this application.

Key Efficacy Findings:[5,6,7] Please refer to the clinical review by Dr. Nicole Gormley for the full review on efficacy and safety. The following is a summary of the key findings from labeling discussions for elotuzumab as of **October 15, 2015**.

Study CA204004 is an open-label, randomized, Phase 3 study of elotuzumab (10 mg/kg IV) with lenalidomide (25 mg orally)/dexamethasone (40 mg orally), compared to lenalidomide alone (Ld), in patients with relapsed and/or refractory multiple myeloma treated with 1 to 3 prior therapies. The co-primary endpoints for this study were overall response rate (ORR) and progression-free survival (PFS). As assessed by the Independent Review Committee (IRC), median ORR was 78.5% in the elotuzumab arm versus 65.5% in the control arm and median PFS was 19.4 months in the elotuzumab arm versus 14.9

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[5] Empliciti (elotuzumab) draft label, October 15, 2015

[6] Empliciti (elotuzumab) Summary of Clinical Efficacy (Section 2.7.3)

[7] Empliciti (elotuzumab) September 15, 2015 Midcycle Meeting Slides

months in the control arm (2.7.3). These results were considered to be clinically meaningful and statistically significant. Secondary objectives were time to first objective response (TTR), duration of response (DOR), and overall survival (OS). The median TTR was 1.9 months in both arms, median DOR was 20.7 versus 16.6 in the control arm, and the median OS was not estimable for the elotuzumab arm but was 34.6 in the control arm (2.7.3).

The baseline demographics and disease characteristics of patients were consistent with a population of advanced stage, refractory multiple myeloma patients in terms of age, gender, disease characteristics, and number and types of prior therapies. The median age for patients in this study was 66 years. Close to 60% of patients were men, 84% were Caucasian, 10% were Asian, and 4% were black. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 (47.1%) or 1 (44%); 9% of patients had ECOG performance status of 2. The majority of patients (70%) had IgG type MM, 53% had Stage II or Stage III multiple myeloma and 53% had >3 lytic bone lesions. All patients had received prior systemic anticancer therapy. Prior therapies included stem cell transplant (55%), bortezomib (70%), melphalan (65%), thalidomide (48%), and lenalidomide (6%), and were well balanced between the E-Ld and Ld treatment groups.

In Study CA204004, a total of 761 patients were enrolled at 230 sites in 22 countries from June 2011 to November 2012 with the majority from Europe (60%). Of the 761 enrolled patients, 646 patients were randomized. Of the 646 patients randomized, 635 (98.3%) were treated (318 with E-Ld and 317 with Ld), and 11 (1.7%) patients were not treated. The patients who were randomized received either elotuzumab (10 mg/kg) administered IV on days 1, 8, 15, and 22 of cycles 1 and 2, and on days 1 and 15 on cycle 3 and beyond in combination with lenalidomide, 25 mg orally, on days 1-21 and dexamethasone, 8 mg IV plus 28 mg, orally. On weeks without elotuzumab, dexamethasone was given 40 mg orally. The above dosage regimen was to be repeated every 28 days until disease progression, unacceptable toxicity or patient met the criteria for withdrawal of study drug as outlined above.

4.2.2 Safety[5,7,8]

The safety of elotuzumab is based on the analysis of data from Study CA204004. Seven hundred and sixty-one patients who received at least one dose of study medication from the primary Study CA204004 was considered for the safety evaluation. Of those 761 patients, 318 patients received E-Ld and 317 patients received Ld.

The median duration of drug exposure was approximately 5 months longer in the E-Ld group than in the Ld group with a median number of treatment cycles of 19 received in the E-Ld group versus 14 in the Ld group arm. As of the clinical database lock, a higher percentage of E-Ld treated patients were still on treatment (35.5%) vs. the Ld-treated patients (20.8%).

The frequency of adverse events (AEs) (any grade and Grade 3-4) were tabulated using the Medical Dictionary for Regulatory Activities by system organ class and preferred terms using either Version 16.1 and 17.0. The intensity of AEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

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[8] Empliciti (elotuzumab) Summary of Safety (Section 2.7.4)

Serious AE's of any grade were reported for 208 patients (65.4%) treated with E-Ld and for 179 patients (56.5%) treated with Ld. In the E-Ld and Ld population, the percentage of patients with Grade 3-4 AEs was 77.7% and 65.6% respectively. The most frequently reported non-hematologic Grade 3-4 events (E-Ld and Ld respectively) in at least 5% of patients were pneumonia (10.4% vs. 7.3%), fatigue (8.5% vs. 8.2%), hyperglycemia (7.2% vs. 4.4%), cataract (6.3% vs. 2.8%), deep vein thrombosis (5.7% vs. 2.2%), diarrhea (5% vs. 4.1%), and back pain (5% vs. 4.4%). Grade 3-4 hematologic abnormalities (E-Ld and Ld respectively) in at least 5% of patients were lymphopenia (76.7% and 48.7%), neutropenia (33.6% and 43.7%), leukopenia (32.4% vs. 25.6%), thrombocytopenia (19.2 vs. 20.3%), and anemia (18.9% vs. 21.2%). Grade 3-4 AEs of infection were reported in 28% of E-Ld and 24.3% of Ld patients. The most common Grade 3-4 AE of infection (>5% frequency, E-Ld and Ld) was pneumonia (10.4% and 7.3% respectively).

In Study CA204004, dose reductions of elotuzumab were not permitted. The only dose modifications of elotuzumab allowed were delays, omission, or infusion interruptions. Dose delays occurred in 186 (58.5%) of elotuzumab-treated patients with 32% having more than 1 delay. If the dose of one drug in the regimen (i.e., lenalidomide, dexamethasone, or elotuzumab) was delayed, interrupted, or discontinued, the treatment with the other drugs was to continue as scheduled. Patients experiencing a 28 day delay in all study drugs (lenalidomide, dexamethasone, and elotuzumab) due to an AE related to study treatment were to be discontinued from study drug. Dose omissions occurred in 176 (55.3%) patients, with 28% having more than 1 omission. The majority of omissions led to an interval of ≥28 days between 2 doses (71.8%). The most common reasons for "other" dose omissions for this trial included, but were not limited to, reasons such as scheduling conflicts, AEs, non-hematologic toxicity, patient did not return for visit, medical monitor did not feel it was in the best interest of the patient to be treated at the time, public holidays, personal or logistical reasons, administrative reasons, lack of study drug supply, dosing error, or patient was on vacation.

Infusion reactions were reported in approximately 10% of patients treated with elotuzumab with lenalidomide and dexamethasone in Study 1. All reports of infusion reaction were ≤Grade 3. Grade 3 infusion reactions occurred in 1% of patients in Study 1. In Study 1, 5% of patients required interruption of the administration of elotuzumab for a median of 25 minutes due to infusion reaction, and 1% of patients discontinued treatment due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) in Study 1 had a reaction during the first dose. For a Grade ≥ 2 elotuzumab infusion-related reaction, the infusion was to be interrupted. Patients with a Grade 4 elotuzumab infusion reaction were to have elotuzumab permanently discontinued. These patients should continue to receive lenalidomide and dexamethasone per protocol. For Grade 2 or 3 infusion reactions, once the elotuzumab infusion-related reaction resolved to Grade ≤ 1, the infusion could be restarted at 0.5 mL/minute. If symptoms did not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to a maximum of 2 mL/minute or the rate at which the infusion reaction occurred. If the elotuzumab infusion reaction recurred, the infusion was to be stopped and not restarted on that day. The infusion could be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication (diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor,

leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated).

Other reasons for elotuzumab infusion interruptions included infusion administration issues (4.4%) and other (5%). A total of 6 patients (1.9%) reduced the IV rate due to an infusion reaction and 8 patients (2.5%) reduced the IV rate due to 'other' reasons. The median duration of infusion interruption due to any reason was 25 minutes.

In this trial, 26.1% of patients in the E-Ld group and 26.8% in Ld group discontinued treatment due to an AE. Grade 3-4 infections (3.5%) represented the highest number of patients who discontinued due to an AE in the E-Ld group and 4.1% in the Ld group. In a clinical trial of patients with multiple myeloma (N=635), opportunistic infections were reported in 22% of patients in the elotuzumab combined with lenalidomide and dexamethasone (E-Ld) arm and 12.9% in lenalidomide and dexamethasone (Ld). The majority of these events were Grade 1 or 2 (18.6% for E-Ld and 11.7% for Ld). Herpes zoster was reported in 6% (n=19) of patients treated with E-Ld and 2.8% (n=9) of patients treated with Ld. None of the events in the E-Ld group were fatal.

In the same clinical trial, invasive second primary malignancies have been observed in 6.9% of patients treated with E-Ld and 4.1% of patients treated with Ld. The rate of hematologic malignancies were the same between E-Ld and Ld treatment arms (1.6%). Solid tumors were reported in 2.5% and 1.9% of E-Ld and Ld treated patients, respectively.

The adverse events of concern were infusion-related reactions, opportunistic infections, and second primary malignancies. These adverse events will be managed in labeling under the Warnings and Precautions section of the label.

Deaths: A total of 94 (29.6%) patients in the E-Ld group and 116 (36.6%) patients in the Ld group died. The majority of all deaths were due to disease progression in both treatment groups (60 patients [18.9%] in the E-Ld group and 78 patients [24.6%] in the Ld group). The other primary causes of death in the E-Ld and Ld groups included infection (16, 5.0% and 9, 2.8%, respectively), cardiovascular disease (3, 0.9% and 7, 2.2%, respectively), and study drug toxicity (5, 1.6% and 6, 1.9%, respectively).

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS.

4.3 ASSESSMENT OF RISK

Despite the available chemotherapy options that include first and second line treatment with lenalidomide, bortezomib, thalidomide, and doxorubicin and third-line treatment options, bortezomib, carfilzomib, pomalidomide, and panobinostat, relapse is inevitable. Since there is no cure, most patients will survive only 3 years after their initial remission from first line multiple myeloma therapy, and it will typically reappear more aggressively after each relapse. The indication for elotuzumab is in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

The anticipated duration of use for elotuzumab is 10 mg/kg administered IV every week for the first two cycles and every 2 weeks thereafter when administered with

lenalidomide and low-dose dexamethasone every 28 days until disease progression, unacceptable toxicity [redacted] (b) (4)

Infusion-related reactions were common between doxorubicin and carfilzomib. However, the infusion-related reactions seen with elotuzumab did not warrant a Boxed Warning as was the case for doxorubicin. In addition to a Boxed Warning for the infusion-related reactions, cardiomyopathy was also included for doxorubicin. Elotuzumab had infections in common with panobinostat and second primary malignancies in common with lenalidomide. Neither risk was included in a Boxed Warning for these drugs.

Other drugs indicated for the treatment of multiple myeloma contain Boxed Warnings and a REMS for mitigation of risks. These drugs are panobinostat, thalidomide, lenalidomide and pomalidomide. However, they are not similar to risks seen with elotuzumab. Panobinostat required a REMS (Communication Plan only) for severe diarrhea, occurring at 25% of treated patients, and cardiac toxicities (severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes). Arrhythmias occurred in 12% of patients receiving panobinostat compared to 5% of patients in the control arm while cardiac ischemic events occurred in 4% of patients treated with panobinostat compared with 1% of patients in the control arm. Thalidomide, lenalidomide and pomalidomide were approved with a REMS that included elements to assure safe use to mitigate embryo-fetal risk. For thalidomide, it was shown that mortality at or shortly after birth had been reported in about 40% of infants.

In addition to the embryo-fetal risk seen with the aforementioned drugs, venous thromboembolism was included in a Boxed Warning and arterial thromboembolism was as well for pomalidomide and lenalidomide. For lenalidomide, hematologic toxicity (neutropenia and thrombocytopenia) was included in the Boxed Warning also.

Myelosuppression (neutropenia and thrombocytopenia) was seen amongst panobinostat, pomalidomide, and bortezomib and are currently in the Warnings and Precautions section of their respective labels.

The adverse events of concern with elotuzumab were infusion-related reactions, [redacted] (b) (4) infections, and second primary malignancies. In order to minimize the effect or extent of patients having infusion-related risks, patients were to be pre-medicated with dexamethasone, diphenhydramine, ranitidine, and acetaminophen. DHP determined these events to be adequately addressed under the Warnings & Precautions section of the label. In comparison with other agents for treatment of multiple myeloma, elotuzumab appeared to have less side effects which only rose to the Warnings & Precautions section of the label.

The efficacy of elotuzumab is comparable to other drugs used for the treatment of patients with multiple myeloma, and is another potential treatment option for the treatment of patients with multiple myeloma, specifically those who have received one to three prior therapies. In Study CA204004, elotuzumab showed improvement in ORR by 13% (78.5% vs. 65.5%) and an improvement in PFS (19.4 months vs. 14.9 months), a difference of approximately 5 months compared to the control arm. These results were considered to be clinically meaningful and statistically significant.

The prescribing population for elotuzumab will be managed by hematologists and oncologists who are familiar with the disease and adverse events seen with drugs used for the treatment of multiple myeloma.

5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

There are no proposed PMR's and PMC's at the time of this writing.

6 CONCLUSION

DRISK and DHP concur that, at this time, a REMS is not necessary to ensure that the benefits outweigh the risks for elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies. The risks associated with elotuzumab will be communicated through professional labeling. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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

/s/

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11/02/2015

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Concur