

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761035Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA #	761035
Applicant	BMS
Date of Submission	June 29, 2015
PDUFA Goal Date	February 29, 2016
Proprietary Name / Non-Proprietary Name	Empliciti/elotuzumab
Dosage Form(s) / Strength(s)	Injection: 300 mg and 400 mg lyophilized powder in a single- (b) (4) vial.
Applicant Proposed Indication(s)/Population(s)	for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4)
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Division Director Review	Ann Farrell, MD
Regulatory Project Manager Review	Natasha Kormanik
Medical Officer Review	Nicole Gormley, MD/Albert Deisseroth, MD, PhD Virginia Kwitkowski, MS/ACNP-BC
Statistical Review	Chia-Wen Ko, PhD
Pharmacology Toxicology Review	Michael Manning, PhD/ Christopher Sheth, PhD/John Leighton, PhD
OPQ Review	Rachel Novak, PhD/Jibril Abdus-Samad, PharmD/ Maria Jose Lopez Barragan, Natalia Pripuzova/Linan Ha, PhD/Ruth Moore/Collen Thomas/Patricia Hughes/Peter Qiu/Sarah Kennett, PhD/Kathleen Clouse, PhD
Microbiology Review	Maria Jose Lopez- Barragan and Natalia Pripuzova
Clinical Pharmacology Review	Olanrewaju Okunsanya, PharmD, MS/Gene Williams, PhD/ Justin Earp, PhD/Nitin Mehrotra, PhD
OPDP	Nisha Patel, PharmD/Kathleen Davis
OSI	Anthony Orenca, MD/Susan D. Thompson, MD/ Kassa Ayalew, MD, MPH
CDTL Review	Albert Deisseroth, MD, PhD
OSE/DEPI	None
OSE/DMEPA	Michele Rutledge, PharmD/Yelena Maslov, PharmD/Lubna Merchant PharmD
OSE/DRISK	Mona Patel, PharmD/Naomi Redd, PharmD/Cynthia LaCivita, PharmD
Other	Justin C Earp/Jiang Liu/Huifang Chen/Qianyu Dang/Michael Li/ Norman L Stockbridge LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Morgan Walker, PharmD, MBA

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma is a hematologic malignancy characterized by a neoplastic proliferation of clonal plasma cells that produce a monoclonal immunoglobulin. Patients may present with signs and symptoms of anemia, bone pain or pathologic fractures, renal insufficiency, fatigue, hypercalcemia, or weight loss. Treatment options for multiple myeloma have significantly improved over recent decades with the approval and introduction of alkylating agents, the use of high-dose therapy in combination with autologous stem cell rescue, and the introduction of new classes of agents such as immunomodulatory agents (thalidomide analogues) and proteasome inhibitors. Despite these advances, patients with multiple myeloma often relapse or develop refractory disease. Multiple myeloma remains an incurable disease with the exception of an allogeneic transplant; however, few patients are candidates for this therapy.

The efficacy of elotuzumab in combination with lenalidomide and dexamethasone was based on the results of a phase 3 trial, which evaluated elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) compared with lenalidomide and dexamethasone alone (Ld). Elotuzumab was administered as a 10 mg/kg dose intravenously every week for the first two cycles then every 2 weeks thereafter until disease progression or unacceptable toxicity. Lenalidomide was to be taken orally once daily for the first 3 weeks of a 4-week cycle. Dexamethasone was to be administered at a weekly dose of 40 mg. The co-primary endpoints of this trial were progression-free survival (PFS) and overall response rate (ORR). The results showed an estimated hazard ratio for PFS of 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; $p=0.0004$). The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm. The ORR was 78.5 % (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm. The overall survival (OS) data at the time of the clinical database cutoff was not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm. Treatment with elotuzumab in combination with lenalidomide and dexamethasone resulted in a clinically meaningful and statistically significant improvement in both PFS and ORR. Nonfatal serious adverse events occurred in 64.1% of patients in the E-Ld arm compared with 55.2% in the Ld arm. The most frequent SAEs higher in the E-Ld arm vs. the Ld arm respectively were: pneumonia, pyrexia, respiratory tract infection, anemia, and acute renal failure. TEAEs that occurred at an incidence $\geq 10\%$ in either arm and had a $\geq 5\%$ higher rate in the E-Ld arm compared with the Ld arm respectively were: diarrhea, constipation, vomiting, fatigue, pyrexia, peripheral edema, nasopharyngitis, upper respiratory tract infection, weight decreased, creatinine increased, decreased appetite, pain in extremity, musculoskeletal pain, headache, peripheral neuropathy, cough, and oropharyngeal pain.

Additional safety issues identified with the use of elotuzumab in combination with lenalidomide and dexamethasone include: infusion reactions, second primary malignancies, hepatotoxicity, infections, and elotuzumab interference with response assessment. Infusion reactions occurred in 10% of patients. Second primary malignancies occurred in 8.2% of subjects in the E-Ld arm compared with 4.7% of subjects in the Ld arm. Hepatotoxicity was also noted in the trial and there was one case that met Hy's law criteria and had biopsy findings consistent with drug-induced liver injury. The safety profile observed with elotuzumab in combination with lenalidomide and dexamethasone is acceptable given that it is designed to treat a life-threatening illness.

The risk:benefit profile was also assessed in the reviews of Drs. Farrell, Deisseroth and Gormley and I concur with their recommendation of approval. The Applicant has provided substantial evidence of effectiveness for elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received 1 to 3 prior therapies to support approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Multiple Myeloma is a symptomatic disease with bone pain, anemia, infection, renal insufficiency, fatigue, hypercalcemia, or weight loss and is associated with significant morbidity and mortality.	Patients with multiple myeloma experience significant morbidity and mortality.
Current Treatment Options	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 5-6 years.	Current treatment options are inadequate to control the disease. Additional therapies with differing mechanisms of action and adverse event profiles are needed.
Benefit	The results of a phase 3 trial (CA204004), which evaluated elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) compared with lenalidomide and dexamethasone alone (Ld). The co-primary endpoints of this trial were PFS and ORR. In study CA204004, a total of 646 patients were enrolled (321 in the E-Ld arm and 325 in the Ld arm). The results showed an estimated hazard ratio for PFS of 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; p=0.0004). The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm. The ORR was 78.5 % (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm. The OS data at the time of the clinical database cutoff was not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm.	The trial results demonstrated a significant improvement in median PFS for the treatment arm containing elotuzumab.
Risk	Safety was primarily based on the results of the phase 3 trial, but was also supported by pooled data from phase 2 trials evaluating elotuzumab in combination with lenalidomide and dexamethasone. Nonfatal serious adverse events occurred in 64.1% of patients in the E-Ld arm compared with 55.2% in the Ld arm. The most frequent SAEs were in the E-Ld arm vs. the Ld arm respectively were: pneumonia, pyrexia, respiratory tract infection, anemia, pulmonary embolism, and acute renal failure. TEAEs that occurred at an incidence $\geq 10\%$ in either arm and had a $\geq 5\%$ higher rate in the E-Ld arm compared with the Ld arm respectively were: diarrhea, constipation, vomiting, fatigue, pyrexia, peripheral edema, nasopharyngitis, upper respiratory tract infection, weight decreased, creatinine increased, decreased appetite, pain in extremity, musculoskeletal pain, headache, peripheral neuropathy, cough, and oropharyngeal pain.	The elotuzumab treatment arm was associated with greater risk of adverse reactions; however, these adverse reactions did not result in increased mortality as the hazard ratio for the preliminary OS result was 0.71. The infusion reaction can be managed through the use of premedication and in some cases post-medication as well.
Risk Management	A REMS is not required. A description of the safety observed in the clinical trial is included in labeling.	Prescribing information includes information about pre-medications for infusion reactions and management of infusion reactions if they occur. The Warnings and Precautions section includes information about the risk of second primary malignancies, hepatotoxicity, infections, and interference with the laboratory testing.

2. Background

On June 29, 2015, Bristol Myers Squibb submitted a Biologic License Application (BLA) for elotuzumab, a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7) for the proposed indication of: treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4)

Breakthrough Therapy Designation was granted on May 12, 2014, for elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma (MM) in patients who have received one or more prior therapies.

This application was given priority review. No monoclonal antibodies directed against SLAMF7 are approved at this time for treatment of multiple myeloma. Elotuzumab is not approved in any country at this time.

3. Product Quality

There are no issues from a CMC perspective that would preclude approval. The product presentation is single- (b) (4) vials containing 300 mg and 400 mg lyophilized powder. *The data provided in the BLA support a (b) (4) month shelf life for drug substance when stored at (b) (4) °C.* CMC provided an overall acceptability recommendation of the drug product and drug substance, and facility inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

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

SLAMF7 is primarily expressed on natural killer cells, and on normal and malignant plasma cells (including myeloma cells). The results of pharmacology studies reviewed suggest elotuzumab exerts anti-myeloma activity through two characterized mechanisms of action, both involving natural killer cells. One mechanism involves direct activation (in a process that includes binding of elotuzumab to SLAMF7 on natural killer cells and involves the Fc region of the antibody). The other mechanism involves elotuzumab binding to SLAMF7 on myeloma cells, and eliciting antibody-dependent cellular cytotoxicity when in the presence of natural killer cells. The combination of elotuzumab and lenalidomide appeared to elicit enhanced activation of natural killer cells in vitro. In vivo antitumor activity was studied in mouse xenograft models, showing the activity of elotuzumab and lenalidomide was greater than the effects of either agent alone.

Human and nonhuman tissue cross-reactivity assessments indicated that elotuzumab does not cross-react with any of the nonhuman tissues tested, which included the common laboratory animal species. A single dose monkey toxicology study examined the potential for off-target effects of infused elotuzumab, and elotuzumab was well tolerated. Nothing adverse was noted in the local tolerance and hemolysis evaluations. Cytokine release was noted in human blood exposed to elotuzumab. The risk of infusion reactions is clearly stated on the label for Empliciti and premedication prophylaxis is recommended (see full prescribing information).

No genotoxicity studies were conducted with elotuzumab (as per ICH S6) and no carcinogenicity were conducted with elotuzumab (as per ICH S6 and S9). The label for Empliciti contains a Warning and Precaution for second primary malignancies observed in patients. Due to the lack of pharmacologically relevant species, and because animal studies of fertility, early embryonic development and pre- and post-natal effect are not generally warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (as per ICH S9), these types of studies were not conducted with elotuzumab.

5. Clinical Pharmacology

There are no issues from a clinical pharmacology perspective that would preclude approval. Based on the primary clinical pharmacology review:

The clinical pharmacology data submitted with this BLA includes data from multiple-dose studies evaluating the efficacy and safety of elotuzumab as a single agent or in combination. The clinical pharmacology submission also includes population PK and exposure-response analyses for efficacy and safety. The population PK model revealed covariate relationships for elotuzumab clearance with baseline M-protein concentrations and body weight. Body weight based dosing is thus justified. Higher M-protein correlated with higher elotuzumab clearance, however the correlation was modest. The exposure-response analysis revealed there was no difference in median PFS between patients with elotuzumab Cavgss in the lowest quartile of elotuzumab exposure (Cavgss < 209 µg/mL) and patients on active control, after controlling for potential confounding factors such as high M-protein, higher B2- microglobulin, ECOG score, and higher LDH levels. Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors. As PFS in patients with Cavgss concentrations less 209 µg/mL was not better than in the control arm, even after adjusting for other risk factors, it appears reasonable to explore options to optimize dose in this subgroup of patients. We are asking for additional analyses to be conducted as a PMC. The results of the ongoing trial CA204006 will be used to conduct exposure-response analyses and determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10 mg/kg).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This BLA is supported by the results of a phase 3 trial (CA204004), which evaluated elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) compared with lenalidomide and dexamethasone alone (Ld). The co-primary endpoints of this trial were PFS and ORR (assessed by the independent review committee (IRC)). In study CA204004, a total of 646 patients were enrolled (321 in the E-Ld arm and 325 in the Ld arm). The results showed an estimated hazard ratio for PFS of 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; p=0.0004). The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm. The ORR was 78.5 % (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm. The OS data at the time of the clinical database cutoff was not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm.

(b) (4)

Study CA204009 enrolled a total of 152 patients (77 in the E-Bd arm and 75 in the Bd arm). The primary endpoint of this trial was investigator-assessed PFS. The trial was designed to be a proof-of-concept trial (b) (4). As such, the comparison was to be evaluated at the one-sided (b) (4) significance level. The efficacy results demonstrated an estimated hazard ratio for PFS was (b) (4) for E-Bd over Bd (b) (4). The median PFS was 9.7 months (b) (4) in the E-Bd arm vs. 6.9 months (b) (4) in the Bd arm. The ORR was (b) (4) % (b) (4) in the E-Bd arm vs. (b) (4) % (b) (4) in the Bd arm. The overall survival data was only descriptive with occurrence of only 40 events at the time of the analysis. The hazard ratio was (b) (4) (b) (4). The median OS was NE (b) (4) in the E-Bd arm vs. (b) (4) (b) (4) in the Bd arm.

8. Safety

The most frequent SAEs were: pneumonia, pyrexia, and respiratory tract infection.

- The most common adverse reactions were: fatigue, diarrhea, pyrexia, constipation, cough, peripheral edema, nasopharyngitis, upper respiratory tract infection, and decreased appetite.
- Infusion reactions occurred in 10% of patients.
- Second primary malignancies occurred in 8.2% of subjects in the E-Ld arm compared with 4.7% of subjects in the Ld arm.
- Hepatotoxicity occurred in the trial and there was one case that met Hy's law criteria and had biopsy findings consistent with drug-induced liver injury.
- Infusion reactions were mitigated by protocol-required premedication schedule and frequent vital sign measurements during infusion.
- Elotuzumab may interfere with the serum electrophoresis (SPEP) and immunofixation (IFE) assays used for assessment of response to treatment.

Nonfatal serious adverse events occurred in 64.1% of patients in the E-Ld arm compared with 55.2% in the Ld arm. The most frequent SAEs were in the E-Ld arm vs. the Ld arm respectively were: Pneumonia, pyrexia, respiratory tract infection, anemia, pulmonary embolism, and acute renal failure. TEAEs that occurred at an incidence $\geq 10\%$ in either arm and had a $\geq 5\%$ higher rate in the E-Ld arm compared with the Ld arm respectively were: diarrhea, constipation, vomiting, fatigue, pyrexia, peripheral edema, nasopharyngitis, upper respiratory tract infection, weight decreased, creatinine increased, decreased appetite, pain in extremity, musculoskeletal pain, headache, peripheral neuropathy, cough, and oropharyngeal pain.

9. Advisory Committee Meeting

This application was not referred to an ODAC as no clinical efficacy or safety issues arose that required an advisory committee meeting and discussion.

10. Pediatrics

Elotuzumab has Orphan Drug Designation for this indication and is therefore exempt from the requirements of PREA.

11. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies: A REMS is not required.
- Other Postmarketing Requirements and Commitments: See action letter.

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/s/

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11/29/2015

RICHARD PAZDUR
11/29/2015