CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761158Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
PDUFA Goal Date	August 05, 2020
OSE RCM #	2019-2432; 2019-2434
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Review Completion Date	August 5, 2020
Subject	Review to determine if a REMS is necessary
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin-blmf 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity belantamab mafodotin-blmf is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline Intellectual Property Development Ltd. (the "Applicant") submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) and is seeking accelerated approval for the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) (b) (4)

Based on the efficacy and safety information, the clinical reviewers stated that belantamab mafodotin-blmf shows clinically meaningful benefit; however, belantamab mafodotin-blmf causes ocular toxicity that can result in changes in the corneal epithelium and changes in vision, including severe vision loss and corneal ulcers. Although the ocular toxicities, including keratopathy, are a known class-effect associated with antibody-drug conjugate (ADCs) containing microtubule-inhibitor payloads, such as monomethyl auristatin F (MMAF), the toxicity observed with belantamab mafodotin-blmf is greater than that observed for other ADCs. The incidence and severity of keratopathy observed in the clinical trials was high (76%) and associated with clinically relevant decreases in visual acuity, including severe vision loss in some patients, and interfered with patients' activities of daily living and impacts on driving and reading. During the clinical trial ophthalmic exams were performed at baseline and prior to dosing to evaluate the change in ocular health, more specifically changes in the corneal epithelium. The exam findings were used to guide changes in treatment that included dose modifications, including dose interruption, dose reduction, and discontinuation of study treatment.

Despite close monitoring with comprehensive ophthalmic exams at baseline and prior to dosing, and implementation of dose modifications, many patients still had recurrent and/or unresolved ocular adverse events. Because many patients had significant keratopathy on ophthalmic exam in the absence of other ocular symptoms, there is also a concern that keratopathy could go undetected in the absence of close monitoring, potentially leading to serious sequelae, including the development of corneal ulcers. The observed changes in the corneal epithelium appear to be reversible in some patients with early detection and dose modifications.

The applicant initially did not submit a REMS with this application but proposed a global risk management plan along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, (b) (4) On January 28, 2020 the Agency notified the Applicant that a box warning and a REMS would be necessary to mitigate the risk of ocular toxicity and on April 13, 2020 the Applicant submitted labeling that included a boxed warning for ocular toxicity, Medication Guide and REMS that comprised of a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ocular toxicity that is associated with the use of belantamab mafodotin-blmf and the proposed risk mitigation strategies is the focus of this review.

Belantamab mafodotin-blmf will be used in both inpatient and outpatient settings such as oncology infusion centers and prescribed by oncologist, hematologist, or other healthcare providers directly involved in the management of MM patients. There is significant concern regarding the ocular toxicity and the management in the post marketing setting. Patients will need to have eye care exams performed prior to each dose, patients may initially be asymptomatic, most prescribers will not be familiar with the corneal adverse reactions and there will be a lack of familiarity with the grading of the corneal reactions in labeling that are based on both corneal examination findings and changes in BCVA. For these reasons the Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) have determined that if approved, labeling is not sufficient to mitigate these risks, and a REMS with ETASU is necessary to ensure the benefits of belantamab mafodotin-blmf outweigh its risk of ocular toxicity. The REMS is comprised of a communication plan to assist with implementation of the REMS and includes the following ETASU: prescriber certification (ETASU A), healthcare setting certification (ETASU B), patient enrollment with documentation of safe use condition (ETASU D) and monitoring (ETASU E).

The goal of the proposed BLENREP REMS is to manage the risk of ocular toxicity by:

1. Ensuring that healthcare providers are educated on the risk of ocular toxicity associated with the use of BLENREP
2. Ensuring that healthcare providers are educated and adhere to the following:
   a. submit documentation that ophthalmic exams are being done at baseline and prior to each dose to identify ocular toxicity
   b. counsel patients on the risk of ocular toxicity and the requirement for monitoring via ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms as described in the Prescribing Information
3. Ensuring safe use of BLENREP by:
   a. Ensuring that BLENREP is infused in certified healthcare settings only after verification of ophthalmic exams
4. Ensuring that patients are informed about:
   a. the risk of ocular toxicity associated with the use of BLENREP
   b. the requirement for ophthalmic exams at baseline, prior to each dose and promptly for worsening symptoms, as described in the Prescribing Information

The timetable for submission for assessment for the REMS requires the Applicant to submit REMS assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS. Depending on the assessment findings, new safety information or other information, FDA may determine it is necessary to modify the REMS or consider other regulatory actions to address new concerns.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) belantamab mafodotin-blmf is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline Intellectual Property Development Ltd. (hereafter referred to as the "Applicant") submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) The Agency has revised the indication to, for the

treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The applicant initially did not submit a REMS with this application but proposed a global risk management plan along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information, (b) (4) On January 28, 2020 the Agency notified the Applicant that a box warning and a REMS would be necessary to mitigate the risk of ocular toxicity and on April 13, 2020 the Applicant submitted boxed warning for ocular toxicity, Medication Guide and REMS that comprised of a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2 Background

2.1 PRODUCT INFORMATION

Belantamab mafodotin-blmf is a NME BLA type 351(a) pathway application.[a] It is a B-cell maturation antigen (BCMA)-directed antibody-drug conjugate. Upon binding to BCMA, belantamab mafodotin-blmf is internalized followed by release of free cytotoxic drug monomethyl auristatin F (cys-mcMMAF) via proteolytic cleavage. The released MMAF intracellularly disrupts the microtubule network, leading to cell cycle arrest and apoptosis.[1] Belantamab mafodotin-blmf is prepared as 100 mg lyophilized powder in a single-dose vial for reconstitution. The recommended dose of belantamab mafodotin-blmf is 2.5 mg/kg intravenously every three weeks over 30 minutes infusion until disease progression or unacceptable toxicity.[b] Belantamab mafodotin-blmf breakthrough therapy designation on October 27, 2017. Belantamab mafodotin-blmf is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for belantamab mafodotin-blmf (BLA 761158) relevant to this review:

- 01/31/2014: Investigation New Drug (IND) 119333 submission for belantamab mafodotin-blmf (GSK2857916) was received.
- 10/27/2017: Breakthrough Therapy designation granted
- 12/05/2019: BLA 761158 submission for belantamab mafodotin-blmf with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) (b) (4) received.
- 01/28/2020: Applicant was informed that the ocular toxicity warrants a boxed warning, and a REMS, and encouraged the Applicant to think about a detailed REMS plan to ensure adequate and frequent assessment of vision.
- 02/11/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data,

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

FDA has determined that a REMS will be necessary to ensure that the benefits of belantamab mafoditin-blmf outweighs the risk of ocular toxicity.

- 02/18/2020: The Applicant submitted communication plan REMS to mitigate the risk of ocular toxicity.
- 03/04/2020: The Agency reiterated its concerns via teleconference regarding the rates/incidence of ocular toxicity observed in the DREAMM-2 trial and how this relates to the overall cumulative impact on clinical safety of belantamab mafoditin-blmf. In addition, the Agency stated that the proposed REMS strategy would need to be more robust and that the Agency required additional information to assess the risk/benefit profile of belantamab mafoditin-blmf with respect to mitigating the risk of ocular toxicity.
- 04/13/2020: The amended submission for BLA 761158 received from the Applicant. The amended submission included the proposed REMS consists of communication plan, ETASU, an implementation system, and a timetable for submission of assessments to mitigate the risk of ocular toxicity.
- 04/28/2020: A teleconference was held between the Agency and the Applicant. The Agency discussed an important deficiency in the proposed REMS submission; communication gap between oncologist and ophthalmologist. The Agency recommended that the Applicant develop a consult form for the Ophthalmologist that includes risk of ocular toxicity with belantamab mafoditin-blmf, ocular toxicity grading by Keratopathy and Visual Acuity (KVA) scale that is found in labeling so that the ophthalmologist can provide recommendations on the severity of the ocular findings to the oncologists to guide dose modifications and mitigate ocular toxicity with belantamab mafoditin-blmf. The Agency reiterated that USPI and REMS document recommendations align with the KVA scale (vs. Common Terminology Criteria for Adverse Events [CTCAE] scale) and dose modifications be based on GSK scale because that was the measure that was used in the clinical trials supporting the BLA.
- 05/07/2020: The Applicant amended submission for BLA 761158, included the REMS document, REMS Supporting Document and REMS Appended Materials.
- 05/12/2020: REMS Oversight Committee (ROC) meeting[c] was held to discuss the REMS with ETASU to mitigate the risk of ocular toxicity for belantamab mafoditin-blmf. The ROC unanimously concurred with DRM/DHM2 recommendation that the REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of belantamab mafodotin-blmf to outweigh the risk of ocular toxicity.
- 06/26/2020: The Agency sent comments on the REMS document, REMS supporting document, REMS materials, and REMS assessment plan.
- 07/10/2020: The Applicant amended submission for BLA 761158, it included the REMS document, REMS Supporting Document and REMS Appended Materials.
- 07/14/2020: The Oncologic Drugs Advisory Committee (ODAC)[2] was convened to discuss whether the demonstrated benefit of belantamab mafodotin-blmf outweigh the risks in the proposed patient population with multiple myeloma. The ODAC vote was 12 “yes” and 0 “no” as answers to the voting question above (2 did not vote). The ODAC panel concluded that the toxicity is certainly not life threatening; in general patients are probably willing to take this risk,

[c] As per the 21st Century Review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Office of New Drugs, Surveillance and Epidemiology, and the Office of Regulatory Policy.

and the REMS that the Applicant has outlined for thorough exams before each dose and a grading system addresses the concerns.

- 07/21/2020: The Applicant amended submission for BLA 761158, it included the REMS Appended Materials.
- 07/22/2020: The Agency sent comments on the REMS materials and attestations for the prescriber, healthcare setting and patient enrollment forms.
- 07/27/2020: The Applicant amended submission for BLA 761158. The amended submission included the REMS Appended Materials and the attestations for the prescriber, healthcare setting and patient enrollment forms, REMS Supporting Document.
- 07/27/2020: The Agency sent comments on the REMS Document, REMS Supporting Document, REMS audit plan and REMS Non-compliance plan
- 07/28/2020: The Agency sent comments on the REMS Materials and REMS assessment plan.
- 07/29/2020: The Applicant amended submission for BLA 761158, it included the REMS Document and REMS Supporting Document.
- 07/31/2020: The Agency sent comments on the REMS Document, REMS Supporting Document, REMS Materials and REMS assessment plan.
- 08/03/2020: The Agency sent comments on the REMS Supporting Document and assessment plan
- 08/05/2020: Applicant amended documents including REMS document, Supporting Document, and all appended materials as full submission.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Multiple myeloma is the second most common hematological malignancy and is characterized by a clonal proliferation of neoplastic plasma cells within the bone marrow.[3,4] An estimated 131,392 Americans in 2016 were living with MM. The expected number of new cases in the United States in 2020 is 32,270[d], with 12,830 expected deaths due to the disease[e]. Five-year survival for patients diagnosed with MM is approximately 53.9%.[5] MM is the most frequent cancer involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival.[3] Multiple myeloma is more common in men than women and among individuals of African American descent. Myeloma is most frequently diagnosed among people aged 65-74 with the average age of 69.[5] Patients with MM experience a variety of disease-related events and symptoms, such as bone destruction leading to pain, height reduction and body shape changes, and bone marrow failure, renal failure, immunodeficiency, as well as the psychosocial burden of a diagnosis of cancer.[6] A deterioration in quality of life is particularly marked in elderly frail patients, who represent approximately 30% of patients with MM.[7]

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment paradigms and outcomes for patients with MM have dramatically changed in the past decade with introduction of several new, more effective, and less toxic therapies and more than doubling of the survival.[8] Over the past decade, use of novel agents, including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) has resulted in improved in response rates and overall survival (OS) for patients with MM.[9] Multiple myeloma treatment has improved remarkably over the last 2 decades with the introduction of autologous stem cell transplantation (ASCT) and the introduction of numerous novel agents, including 3 generations of immunomodulator agents (thalidomide[10], lenalidomide[11], and pomalidomide[12]), 2 generations of proteasome inhibitors (bortezomib[13], then carfilzomib[14] and ixazomib[15]) and most recently, the anti-CD38 antibody (daratumumab[16]) and anti-signaling lymphocytic activation molecule F7 (anti-SLAMF7) antibody (elotuzumab[17]). The IMiDs, thalidomide, lenalidomide and pomalidomide are approved with REMS to mitigate the risk of teratogenicity.[10,11,12] The 2019 National Comprehensive Cancer Network (NCCN) guidelines[18] for multiple myeloma list the following combinations as preferred regimens for primary induction therapy in patients who are candidates for transplantation:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone (preferred initial treatment in patients with acute renal insufficiency)

Other recommended regimens, according to the NCCN, are as follows:

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone (category 2B)

Primary therapy for non-transplant candidates are as follows:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Daratumumab/lenalidomide/ dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone

Other NCCN-recommended regimens for these cases include the following:

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab/bortezomib/melphalan/prednisone (category 1)

The introduction of novel agents that target both the tumor cell and its microenvironment[19] (surrounding blood vessels, immune cells, fibroblasts, signaling molecules and the extracellular matrix (ECM)) into the treatment of MM has considerably improved outcomes and it is now possible to aim for deep responses in a greater number of patients in an attempt to prolong remission duration and OS.[20] Despite substantial progress, MM remains a highly resistant disease given its propensity for clonal heterogeneity and its complex interaction with the surrounding bone marrow microenvironment.[21] Almost all patients eventually relapse despite therapeutic responses to a PI, IMiD or both.[22] Treatment for these patients with relapsed or refractory multiple myeloma (RRMM) is complex and there remains no consensus on a clear treatment algorithm.[23] In the last line of therapy for RRMM only one combination regimen of selinexor plus dexamethasone is approved[24] which offers responses of 26.2% in patients with a median duration of response (DoR) of 4.4 months.[25,26] There is a clear need for therapeutic strategies that encompass multiple modes of action.

4 Benefit Assessment

The efficacy of belantamab mafodotin-blmf was evaluated in DREAMM-2, an open-label, multicenter study (NCT 03525678). Eligible patients had relapsed or refractory multiple myeloma, had previously received 3 or more prior therapies, including an anti-CD38 monoclonal antibody, and were refractory to an immunomodulatory agent and a proteasome inhibitor. Patients received either belantamab mafodotin-blmf 2.5 mg/kg or 3.4 mg/kg by intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity. A total of 97 patients received belantamab mafodotin-blmf at a dose of 2.5 mg/kg administered intravenously once every 3 weeks.[1]

The following section is a summary of relevant efficacy information to date for belantamab mafodotin-blmf. The major efficacy outcome measure was overall response rate (ORR) as evaluated by an Independent Review Committee (IRC) based on the IMWG Uniform Response Criteria for Multiple Myeloma. For the primary analysis, the median follow-up was 6.3 months in 2.5 mg/kg cohort as of June 21, 2019. The ORR (PR or better as assessed by the IRC) as assessed by IRC was 31% (97.5% CI: 20.8, 42.6) is shown in Table 1.[1,26,f] Overall, the ORR as assessed by IRC was concordant with the investigator-assessed ORR. The median time to response was 1.4 months (95% CI: 1.0,1.6), and the median time to best response was 2.1 months (95% CI: 1.4,2.2).

Table 1: Efficacy in DREAMM-2[1,26]

	Belantamab mafodotin-blmf N = 97
Overall response rate (ORR), n (%) (97.5% CI)	30 (31%) (21%, 43%)
Stringent complete response (sCR), n (%)	2 (2%)
Complete response (CR), n (%)	1 (1%)
Very good partial response (VGPR), n (%)	15 (15%)
Partial response (PR), n (%)	12 (12%)
Median duration of response in months[a] (range)	NR [NR to NR]
[a]NR= Not reached	

At the time of data cut-off with a median follow-up of 6.3 months, the median duration of response (DoR) (per IRC assessment) was not reached. At the time of the primary analysis, the median progression free survival (PFS) was 2.9 months in the 2.5 mg/kg cohort. The OS was not yet mature at the time of analysis.[1,26]

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for belantamab mafodotin-blmf. The safety of belantamab mafodotin-blmf was evaluated in DREAMM-2 (see Section 4: Benefit Assessment)[1]. A total of 95 patients received belantamab mafodotin-blmf at the recommended dosage

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

of 2.5 mg/kg administered intravenously once every 3 weeks. Among these patients, 22% were exposed for 6 months or longer.[1]

The most common adverse reactions (≥20%) are keratopathy (71%; corneal epithelium change on eye exam), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%).[1]

Deaths

As of the data cut-off for the primary analysis, 33% of patients in the 2.5 mg/kg cohort and 31% of patients in the 3.4 mg/kg cohort had died, mostly due to progressive disease. Most of these deaths occurred >30 days after the last dose of study drug and were attributed to the disease under study by the investigator (26% in the 2.5 mg/kg cohort and 23% in the 3.4 mg/kg cohort). In the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively, there were 3 (cardiac arrest, sepsis and pneumonia) and 7 (cerebral hemorrhage, pneumonia, viral infection, hemophagocytic lymphohistiocytosis, cardiac arrest, pneumonia and acute myeloid leukemia) patients with fatal SAEs. Of these, 1 patient in 2.5 mg/kg cohort and 1 patient in 3.4 mg/kg cohort had a fatal SAE considered related to study drug: the patient in the 2.5 mg/kg cohort had sepsis, and the patient in the 3.4 mg/kg cohort had hemophagocytic lymphohistiocytosis.[26]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 40% of patients who received belantamab mafodotin-blmf. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).[1]

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received belantamab mafodotin-blmf; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.[1]

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received belantamab mafodotin-blmf. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).[1]

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%), and thrombocytopenia (5%).[1]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 OCULAR TOXICITY

In the pooled safety population, ocular adverse reactions occurred in 77% of the 218 patients. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%) and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (2 lines or more Snellen Visual Acuity change in any eye), and 34% had both ocular symptoms and visual acuity changes. Keratopathy was reported as Grade 1 in 7% of

patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 62 days (range: 11 to 253 days). A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved, and the median duration was 22 days (range: 15 to 22 days).[1]

Overall, 71% of patients in the 2.5 mg/kg cohort (3.4 mg/kg cohort, 77%) experienced keratopathy as reported from the eye examination. Most keratopathy events were diagnosed within the first 2 treatment cycles. By the end of Cycle 2, the cumulative incidence of all corneal events was 54% and 71% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. Most events were Grade 2 or Grade 3 in both cohorts, and Grade 4 events (defined as corneal ulcer) occurred at a low incidence (0 in 2.5 mg/kg cohort; 1% in 3.4 mg/kg cohort). In the 2.5 mg/kg cohort, 62% (59/95) of patients experienced Grade 2 or above corneal exam findings (keratopathy), with a median time to onset of the finding of 36.0 days (range: 19–143) (3.4 mg/kg cohort: 71% of patients [70/99], with median time to onset of 22.5 days [range: 9–150]). Overall in the 2.5 mg/kg cohort, 66% (39/59) of patients recovered from the first occurrence, with median time to resolution of 78 days (3.4 mg/kg cohort: 64% [45/70], with median time to resolution 80 days). Among those with Grade ≥ 2 findings, 39% (23/59) of patients in the 2.5 mg/kg cohort and 33% (23/70) of patients in the 3.4 mg/kg cohort had more than 1 event. As of the last follow up for 2.5 mg/kg cohort, 41% of patient recovered. Of the 59% who had ongoing corneal events, 29% were still on treatment, 7% were in follow-up and in 24% the follow up ended due to death, withdrawal from study or lost to follow up (patient unwilling to have further ocular examination) (3.4 mg/kg cohort: 43% recovered; of the 57% not recovered; 23% on treatment; 9% in follow-up, 26% not resolved when follow up ended). In both dose cohorts, 17% of patients had a treatment-emergent decline in BCVA to 20/50 or worse (a level at which patients may not be legally able to drive, depending on the state) in the better seeing eye. In addition, one patient in the 2.5 mg/kg cohort (with baseline BCVA in one eye that was worse than 20/400) and 2 patients in the 3.4 mg/kg cohort had a decline in BCVA to 20/200 (a level considered legally blind in the U.S.) in the better seeing eye. Based on these results, clinical reviewer stated that keratopathy had a significant impact on patients' vision, including severe vision loss in some patients.[26]

The risk of ocular toxicity was identified as a serious risk in clinical trials and was mitigated by conducting baseline and periodic ocular exams. Screening examination to include BCVA (best-corrected visual acuity), slit lamp examination (with special focus on cornea), intraocular pressure, and dilated fundoscopic examination performed by an ophthalmologist / optometrist up to 21 days prior to first dose and within 3 days prior to each subsequent dosing for the first 4 cycles or more frequent in case of symptoms. After 4 cycles, if asymptomatic and clinically stable, participants may have the frequency of ophthalmic exams decreased to once every 3 months. Dose reductions and treatment interruptions if needed based on the results of these exams.[27]

Labeling recommends conducting ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms; perform the follow-up examinations at least 1

week after the previous dose and within 2 weeks prior to the next dose. Labeling also instructs to withhold belantamab mafodotin-blmf until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at a reduced dose based on severity and to consider discontinuing in patients who develop a Grade 4 corneal adverse reaction. The labeling will include a Boxed Warning stating that belantamab mafodotin-blmf caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss, and symptoms such as blurred vision and dry eyes. Monitoring and dosage modifications for toxicities to address the safety issues with belantamab mafodotin-blmf will be included in Boxed Warning, Warnings and Precautions and the Dosage and Administration section of the label.[1]

Because of the serious risk of ocular toxicity, a REMS is necessary to ensure the benefits of belantamab mafodotin-blmf outweigh this risk.[1] A discussion on the proposed REMS is included in section 7.

5.2 THROMBOCYTOPENIA

In the pooled safety population, thrombocytopenia occurred in 69% of 218 patients, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Fatal adverse reactions included cerebral hemorrhage in 2 patients.[1] The primary cause of death for the first patient was disease progression. The investigator considered that there was a reasonable possibility that the thrombocytopenia may have been caused by belantamab mafodotin-blmf.[28] The cause of death was reported as central brain herniation from obstructive hydrocephalus, hematoma compressing the brain stem from coagulopathy due to thrombocytopenia secondary to multiple myeloma for the second patient.[28] In the 2.5 mg/kg pooled data, 35 (34%) participants experienced a thrombocytopenic event. Thrombocytopenic events were reported as Grade 3/4 events for 20 (19%) participants.[29] Labeling instructs to perform complete blood cell counts at baseline and during treatment as clinically indicated and also recommends considering withholding and/or reducing the dose based on severity. Monitoring and dosage modifications for toxicities to address the safety issues with belantamab mafodotin-blmf will be included in both the Warnings and Precautions and the Dosage and Administration section of the label.[1]

5.3 INFUSION-RELATED REACTIONS

In the pooled safety population, infusion-related reactions (IRR) reported in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Labeling instructs to monitor patients for infusion-related reactions. Labeling also recommends interrupting the infusion and provide supportive treatment for Grade 2 or 3 reactions. In the 2.5 mg/kg pooled data, 21 (20%) participants experienced an IRR. IRRs were reported as Grade 3/4 events for 3 (3%) participants. The median time to onset of the first occurrence of an IRR was 1.0 day and the median duration was 1.0 day. Most IRRs (90%) occurred after the first dose of belantamab mafodotin-blmf, whilst 2 participants experienced their first IRR following the second dose. Labeling instructs to monitor patients for infusion-related reactions and also instructs to interrupt the infusion and provide supportive treatment for Grade 2 or 3 reactions. Labeling recommends resuming at a lower infusion rate and administer premedication for all subsequent infusions, once symptoms resolve. Monitoring and dosage modifications for toxicities to address the safety issues with belantamab mafodotin-blmf will be included in both the Warnings and Precautions and the Dosage and Administration section of the label.[1]

5.4 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, belantamab mafodotin-blmf can cause fetal harm when administered to a pregnant woman. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during treatment with belantamab mafodotin-blmf for 4 months after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

If approved, belantamab mafodotin-blmf is expected to be used in both inpatient and outpatient settings such as oncology infusion centers. It is expected that oncologists/hematologists, who should be familiar with the management of common toxicities associated with MM treatment such as thrombocytopenia, infusion-related reactions and embryo-fetal toxicity, will be the likely prescribers of belantamab mafodotin-blmf. However, ocular toxicity is a serious and concerning risk with MM treatment, and oncologists likely do not have experience in monitoring and managing these types of toxicities.

7 Risk Management Activities Proposed by the Applicant

To mitigate the risk of ocular toxicity, the Applicant submitted prescribing information that contained a boxed warning for the risk of ocular toxicity, a Medication Guide as part of labeling, and a REMS with ETASU.

The Medication Guide, which will be part of labeling, is not a required element of the REMS, it contains information for the patient on the risks that are included in labeling. The Medication Guide will be available on the Blenrep product website or Blenrep REMS website.

7.1 REVIEW OF APPLICANT'S PROPOSED REMS

The applicant initially did not submit a REMS with this application but proposed a global risk management plan along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information (b) (4) Based on teleconference on January 28, 2020 and March 4, 2020 the Applicant agreed to including in labeling a boxed warning for ocular toxicity and a Medication Guide. They also submitted a REMS that is comprised of: a CP and ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) ETASU E (monitoring), an implementation system, and a timetable for submission of assessments on April 13, 2020.

The Applicant's proposed REMS was in part based on the protocol that was used for monitoring during the clinical development program and the reported adverse events. In response to comments sent by the Agency on June 26, July 22 July 27, July 28, July 31 and August 4, 2020, the proposed REMS was amended on July 7 (email), 10 (Global Submit; GS), 17 (email), 21 (GS), 24 (email), July 27 (docuBridge), July 29 (email), July 30 (docuBridge) and August 4 (email) 2020. The final REMS document, REMS materials and REMS Supporting document was submitted on August 5, 2020. Below is the overview of

the Applicant's proposed REMS, submitted on April 13, 2020 and May 7, 2020 and the changes made during the review of the application.

7.1.1 REMS Goals

The Applicant's proposed goals for the REMS as submitted on April 13, 2020 and May 7, 2020, were as follows:

The goal of the BLENREP REMS is to manage the risk of (b) (4) by:

1. (b) (4)
2. Ensuring safe use of BLENREP by:
    a. (b) (4)
    b. Ensuring that BLENREP is infused in certified healthcare settings only after verification of ophthalmic examination
3. Ensuring that patients are informed about:
    a. the risk of (b) (4) associated with the use of BLENREP
    b. the requirement for (b) (4) ophthalmic examinations at baseline, prior to each dose and promptly for worsening symptoms, as described in the Prescribing Information
4. (b) (4)

Reviewer's Comments: *The Applicant amended the goals to the proposed Blenrep REMS on August 5, 2020, based on previous comments from the Agency on June 26, 2020 to remove the 4th objective. It is not necessary to specifically call out patient enrollment as a separate objective, the enrollment is the mechanism used to meet the 3rd objective.*

The goal of the BLENREP REMS is to manage the risk of ocular toxicity by:

1. *Ensuring that healthcare providers are educated on the risk of ocular toxicity associated with the use of BLENREP*
2. *Ensuring that healthcare providers are educated and adhere to the following:*
    a. *submit documentation that ophthalmic exams are being done at baseline and prior to each dose to identify ocular toxicity*
    b. *counsel patients on the risk of ocular toxicity and the requirement for monitoring via ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms as described in the Prescribing Information*
3. *Ensuring safe use of BLENREP by:*
    a. *Ensuring that BLENREP is infused in certified healthcare settings only after verification of ophthalmic exams*
4. *Ensuring that patients are informed about:*
    a. *the risk of ocular toxicity associated with the use of BLENREP*

b. *the requirement for ophthalmic exams at baseline, prior to each dose and promptly for worsening symptoms, as described in the Prescribing Information*

Reviewer comments: *The REMS goal and objectives are acceptable and align with the REMS requirements.*

7.1.2 Communication Plan

The Applicant proposed to send a Dear Healthcare Provider REMS Letter, a Professional Society Letter, a Fact Sheet (b) (4) to communicate that Blenrep is approved with REMS to mitigate the risk of ocular toxicity. The Applicant proposes to send the Factsheet with the REMS Letters and provide them during the initial discussion with healthcare providers for 12 months after Blenrep approval. The Factsheet messaging focuses on the risk of ocular toxicity and the REMS program. The Healthcare Provider letter and REMS Factsheet would target healthcare providers such as oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, pharmacists and eye care professionals. The REMS Letters to Professional and REMS Factsheet targets professional societies such as; American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), Advanced Practitioner Society for Hematology and Oncology (APSHO), Oncology Nursing Society (ONS), National Comprehensive Cancer Network (NCCN), Society of Hematologic Oncology (SOHO) and Hematology Oncology Pharmacy Association (HOPA). The Applicant will send the REMS letter by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable. In addition, they proposed to disseminate a similar letter to ophthalmology professional societies and associations. The Applicant proposed to email the REMS Letters within 30 calendar days of the date Blenrep is first commercially distributed, and again 12 months later. (b) (4)

(b) (4)

Reviewer comments: *We agree with the Applicant's proposal that is it necessary to communicate the serious risks of Blenrep, and that Blenrep is only available through a restricted distribution program (Blenrep REMS). Information on the REMS in these communication pieces will include the requirement that prescribers must certify in the REMS program prior to prescribing Blenrep, the requirement that healthcare setting must certify in the REMS program prior to dispensing Blenrep, and the need for monitoring patients enrolled in the REMS program.*

Since eye care professionals are not included as stakeholders in the REMS, we have determined that the Healthcare Provider REMS Letter should only be sent to the healthcare providers, likely to prescribe, dispense or administer Blenrep, such as oncology nurses and pharmacists.

We also did not agree with the Applicant's proposal (b) (4) *was necessary.* (b) (4)

(b) (4)

(b) (4) *We asked the Applicant to remove this material as part of the REMS and they agreed.*

(b) (4)

(b) (4)

The Applicant's proposed timelines for the communications are acceptable. Comments on the letters were shared with the Applicant on July 26, 2020 and July 31, 2020. The letters submitted on August 5, 2020 are acceptable.

7.1.3 Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber and healthcare setting certification, patient enrollment with documentation of safe use condition and monitoring.

ETASU A: Prescriber Certification: Prior to prescribing the product, the healthcare provider must certify in the Blenrep REMS. To become certified, the prescriber must review the prescribing information, the Program Overview and Education Program for Prescribers, successfully complete the Knowledge Assessment, enroll in the REMS by completing the Prescriber Enrollment Form, and submit these to the REMS program. The prescriber must agree to counseling the patient on the risks associated with Blenrep, including the ocular toxicity and the requirement for monitoring via ophthalmic examinations (e.g., visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms by providing a copy of the Patient Guide that outlines the risk of ocular toxicity of Blenrep to the patient. The prescriber must also agree to consult an eye care professional to perform and complete the ocular exams and to complete a Patient Status Form prior to each dose.

Reviewers comments: *We agree with the Applicant's proposal that it is necessary to require prescriber training and certification as part of the REMS; it ensures that prescribers are educated on the approved indication, risks of ocular toxicity associated with the use of Blenrep, the need for monitoring via ophthalmic examinations at baseline, prior to each dose, and promptly for worsening symptoms and dosage adjustment if necessary, and the need to counsel patients on the risk before prescribing Blenrep. We also agree with the requirements for certification as listed above.*

On April 28, 2020, we conveyed to the Applicant, that before treatment initiation the REMS should include that the prescriber needs to assess the patient's ocular health by consulting an eye care professional to perform and complete visual acuity and slit lamp using the Eye Care Professional Consult Request Form. The consult form is to assist the oncologist in managing corneal toxicities by facilitating the findings of the eye exam and connect these findings to the recommendations for dosage modifications as outlined in section 2 (Dosage Modifications for Adverse Reactions) of labeling. The ophthalmologist can communicate the findings to the prescriber using the Eye Care Professional Consult Request Form, the form should align with section 2 of labeling, including Table 1. Dosage Modifications for Corneal Adverse Reactions per the Keratopathy and Visual Acuity (KVA) Scale.

The Applicant submitted a proposed Eye Care Professional Consult Request Form on May 7, 2020. We agree with the Applicant's proposal to record the findings of the eye exam in Eye Care Professional Consult Request Form; however, we recommended they add a summary of worst finding in the worst affected eye as this aligns with section 2 of labeling and to assist in determining the grade of toxicity. We also recommended that to include "Normal" as a grading scale category and a column with check boxed for reporting the grade for the worst eye. We understand this is not included in labeling, this was a

recommendation from the Division of Ophthalmology (DO) so the eye care profession can record a normal finding.

On July 22 and July 28, 2020, we provided feedback on the attestations included in the Prescriber Enrollment Form. As a condition of certification, prescribers must attest on the Prescriber Enrollment Form that they agree to comply with the Blenrep REMS requirements. Before treatment initiation they must counsel patients on the risk of ocular toxicity, requirement for monitoring via ophthalmic examinations at baseline, prior to each dose, and promptly for worsening symptoms, enroll the patient by completing and submit the Patient Enrollment Form to the Blenrep REMS. They also agree to comply with the Blenrep REMS requirements before each infusion, which includes that assess the patient's ocular health by consulting an eye care professional to complete visual acuity and slit lamp using the Eye Care Professional Consult Request Form, assess the patient's ophthalmic consult results for appropriateness of continuing treatment and document and submit to the REMS Program using the Patient Status Form.

ETASU B: Healthcare Setting Certification: The Applicant proposed that Blenrep is dispensed only in healthcare settings that are certified. Certified healthcare settings will be required to verify that healthcare prescribers are certified, patients are enrolled and authorized to receive the dose of Blenrep prior to administering Blenrep to patients. Healthcare Setting must become certified by designating an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the Healthcare Setting. To become certified, the authorized representative must review the Prescribing Information, Program Overview, and Education Program for Healthcare Settings and enroll in the REMS Program by completing the Healthcare Setting Enrollment Form and submitting it to the REMS Program. Prior to administering Blenrep to patient, the healthcare setting must obtain authorization to dispense each dose by contacting the REMS Program to verify that the prescriber is certified, and the patient is enrolled and authorized to receive the drug. This verification will be captured within the REMS Checklist online or be documented on the REMS Checklist for each patient who received Blenrep. The completed REMS Checklist must be provided to the BLENREP REMS within 5 business days of infusion.

***Reviewer comments**: FDA agrees with the Applicant's proposal for healthcare setting certification to ensure that healthcare prescribers are certified, patients are enrolled and authorized to receive the dose of Blenrep prior to administering Blenrep to patients. The certification of the Healthcare setting helps to close this loop in the REMS and the Healthcare Setting Enrollment Form is used to implement and support this ETASU. On July 22, 2019 we provided feedback on the attestations included in the Healthcare Setting Enrollment Form. For the authorized healthcare setting representative these attestations include complying with reviewing the Prescribing Information, Program Overview and Education Program for Healthcare Settings, and agreeing to use the Program Overview and Education Program for Healthcare Settings to train all relevant staff involved in dispensing of Blenrep. The authorized healthcare setting representatives must establish processes and procedures to the REMS Checklist is completed and submitted for each patient. As a condition of certification, the authorized healthcare setting representatives must oversee the implementation and compliance with Blenrep REMS requirements at their healthcare setting, including that before dispensing Blenrep, the healthcare setting staff must obtain authorization before administering each dose by contacting the Blenrep REMS to verify that the REMS program requirements have been met (the prescriber is certified, the patient is enrolled and authorized to receive the dose of Blenrep (REMS program has received the Patient Status Form documenting eye exam was performed) and complete the REMS Checklist. The authorized healthcare setting representatives must submit the REMS Checklist to the Blenrep REMS. In addition, the authorized pharmacy representative will comply with the following REMS requirements at all times:*

- *Not re-distribute, transfer, loan or sell BLENREP.*
- *Maintain records documenting staff completion of REMS training.*
- *Maintain records that all processes and procedures are in place and are being followed.*
- *Comply with audits carried out by GlaxoSmithKline or third party acting on GlaxoSmithKline's behalf to ensure that all processes and procedures are in place and are being followed.*

The titles of each section of the REMS template must be maintain as they align with the statute and support standardization of the format and content of a REMS document. We conveyed to the Applicant on July 27, 2020 to keep "dispense" in the title and the word "administer" in the text for further clarification regarding the infusion of the drug.

The Applicant has made all the necessary changes and they are acceptable.

ETASU D: Patient enrollment with documentation of safe use condition: The Applicant proposed that Blenrep be dispensed only to patients, who are enrolled in the REMS program and that the prescriber complete a Patient Status Form prior to each dose. This ensures that patients are educated on the risk of ocular toxicity of Blenrep, the need for monitoring, and that the results of the eye exam are documented prior to the patients receiving their next dose of Blenrep.

Reviewer Comments:
Patient enrollment: We agree that patient enrollment is necessary to ensure that patients are informed of the risks and the need for monitoring. On July 22, 2019, we provided feedback on the attestations included in the Patient Enrollment Form. These attestations include before starting the treatment, the patient must comply with receiving counseling from the prescriber using the Patient Guide, enroll in the Blenrep REMS by completing the Patient Enrollment Form with the prescriber and get an eye exam during the treatment and before each infusion. In addition, the patient will comply with the following REMS requirements at all times:

- *Patient must inform the prescriber if they have any signs or symptoms of worsening eyesight or eye health including, blurry vision, dry eyes, worsening vision*
- *Patient must understand GlaxoSmithKline and its agents may use and share the personal information to enroll the patient into and manage the Blenrep REMS. Information about all patients who get Blenrep will be stored in a private and secure database. Patient's health information may be shared with the U.S. Food and Drug Administration (FDA) to evaluate the Blenrep REMS; however, name of the patient will not be shared.*
- *Patient must give permission for the GlaxoSmithKline and its agents to contact them or their prescriber by phone, mail, or email to manage the Blenrep REMS.*

Patient Status Form: On July 27, 2020, the Applicant submitted the proposed Patient Status Form, which includes data fields to record details from the results of the corneal examination. Each time the Patient Status Form is completed, the prescriber will be required to record the findings for each eye to include: mild, moderate and severe superficial keratopathy, corneal epithelial defects, and changes in the BCVA from baseline (per Snellen Visual Acuity) and well as any additional corneal examination findings.

The review team which consists of DMH2, DRM and DO discussed several times throughout the review of the application what information was needed on the Patient Status Form to ensure that the eye exam had been performed, the results could be applied to determine the grade of the ocular toxicity and that appropriate actions were taken to mitigate the risk of the ocular toxicity. Initially the review team had determined that the prescriber would only need to report the grade of ocular toxicity which would guide the prescriber to determine if dose modifications were necessary based on recommendations in labeling. DRM discussed the potential burden it may place on the prescriber to transcribe the eye-specific detailed findings from the Eye Care Professional Consult Request Form to the Patient Status Form. The review team did not believe that including the information on the form was necessary for the prescriber to determine the grade of ocular toxicity. Recommendations on what to include on the form was conveyed to the Applicant on two different occasions (July 22 and July 31, 2020).

The Applicant wanted to retain the following as required data fields on the Patient Status form: corneal examination findings for each eye: mild, moderate and severe superficial keratopathy, corneal epithelial defects, and changes in the BCVA from baseline (per Snellen Visual Acuity) and well as any additional corneal examination findings. On August 3, 2020, the review team had a teleconference with the Applicant to better understand their rationale for including these date fields. The Applicant stated that they wanted to capture the details of the eye exam to connect the exam findings, to the grade of ocular risk and appropriate dose modifications. They had communicated that the Blenrep REMS database is built to capture the Patient Status Form entries to facilitate both the REMS data and the pharmacovigilance (PV) reporting.

Following discussion with the Applicant, DMH2 and DO agreed that there was value including these fields as it could help the prescriber with determining the grade of ocular toxicity and if the grading, determined by the prescriber, aligned with what is described in labeling. In support of its position, DHM2 and DO note that these details are necessary to determine whether the KVA scale is being used properly. DRM felt that transcribing of this information (i.e., results of Eye Specialist Consult Form to the Patient Status Form) introduces administrative burden to the prescriber that has the potential to impede patient access should the prescriber refuse to complete this information or if information from the form is missing. DRM and OMEPRM maintain that collection of the grade of toxicity and the particular dose modification, if any, is necessary to ensure safe use of the drug. DRM does not oppose a logic model that would guide the prescriber from making an appropriate grading of ocular toxicity based upon entry of the results of the ocular exam nor do we oppose the collection of information from the eye exam as part of the enhanced PV activities. However, the REMS Patient Status Form is not designed in a way that allows for entry of specific results from the exam that can be used for real-time clinical decision support to guide the grade of ocular toxicity. At this time, the program requires transcribing information from the consult form to the Patient Status form. The prescriber then separately makes a determination of grade of toxicity based upon the guidelines in the labeling at in the table at the Patient Status Form.
DRM also believes that the Applicant can take responsibility of following up with the eye care specialist regarding the specific eye exam results as part of their PV or PMR activities.

After discussion between the DMH2, DRM and DO on August 3, 2020, as well as a discussion with and advice from the ROC on August 4, 2020, it was decided that this level of detail from the eye exam should be collected on the Patient Status Form. Based on previous feedback from stakeholders that participate in other REMS, DRM does not agree with this advice but is willing to align with this decision. The Assessment Plan will include an evaluation of the burden of the REMS and to determine if future modifications are warranted to improve efficiencies and reduce burden.

The Applicant has made all the necessary changes and they are acceptable.

ETASU E: Monitoring: The Applicant proposed the requirement for monitoring the ocular toxicity is ophthalmic examinations (e.g., visual acuity and slit lamp) at baseline, prior to each dose, promptly for worsening symptoms and to make dosage adjustments based on the results of these exams if necessary.

Reviewer comments: *FDA agrees with the Applicant's proposal of the need for monitoring to prevent or reduce the severity of the ocular risk by requiring an exam prior to each dose of Blenrep, which may identify early asymptomatic ocular toxicity and mitigate this risk before it progresses. The Patient Status Form supports this ETASU and as designed should ensure this requirement is met. The ophthalmic examinations (visual acuity and slit lamp) needs to be performed at baseline, within 2 weeks prior to each dose, and promptly for worsening symptoms as needed in accordance with the Prescribing Information.*

The Prescriber and Patient enrollment forms are also support this ETASU, when prescribers and patients sign their respective forms, they agree to comply with the requirements for monitoring. The Applicant has made all the necessary changes and they are acceptable.

7.1.4 Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Call Center to support patients, prescribers, healthcare settings and wholesalers in interfacing with the REMS. The Applicant will establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Blenrep REMS Program. The Applicant will ensure that Blenrep is only distributed to certified healthcare settings, by wholesalers who are compliant with distributing Blenrep as per outlined in the REMS program. To ensure compliance with the REMS, the Applicant will maintain processes and procedures to maintain adequate records to demonstrate that REMS requirements are met (including but not limited to records of: drug distribution and administration; certification of prescribers and healthcare settings; enrolled patients; and audits of healthcare settings and wholesalers-distributors). These records must be readily available for FDA inspections. The Applicant will establish monitoring and audit procedures on an ongoing basis to ensure that the requirements of the REMS are being met and take corrective measures if non-compliance is identified.

The high-level process flow for the Blenrep REMS portal is described as follows:

- The certified prescriber will log into the website and select the appropriate patient and, complete the patient status information based on results from the eye exam. (b) (4) (b) (4)

- The Healthcare Setting can log into the website and verify that the patient is eligible for infusion, generate an authorization code and confirm the date and amount of drug dispensed. REMS Checklist need to complete and submit to the REMS Program within 5 business days of administration. (b) (4) (b) (4)

***Reviewer's comment**: We agree with the Applicant's proposal to include an implementation system. We provided comments on June 26, 2020 that we have inserted the language regarding the accessibility of the database. The Applicant must provide prescribers access to the database of certified healthcare settings and their enrolled patients. The Applicant must also provide authorized wholesalers-distributors access to the database of certified healthcare setting. The Applicant accepted these revisions, with one minor revision proposed as follows:* (b) (4) *The Agency denied the revisions* (b) (4) *the proposed* (b) (4) *language* (b) (4) *can be explained in REMS Supporting Document, but in REMS Document, the language "database" needs to be maintained.*

We did not agree with the Applicant's proposal (b) (4) *We initially added that healthcare settings be audited no later than 90 calendar days after they become certified and annually thereafter. We also changed the requirements to audit all wholesalers-distributors for no later than 90 calendar days after they become authorized to distribute the drug and annually thereafter to align with current REMS practices and to ensure REMS process and procedures are in place, functioning, and support the REMS program requirements.*

The Applicant proposed (b) (4) (b) (4) (b) (4) *Therefore, we recommended that they audit all certified healthcare settings no later than 90 calendar days after they have dispensed Blenrep, and once every 3 years thereafter. Because some healthcare settings may order but not dispensed Blenrep, DRM wanted to capture healthcare settings that have dispensed Blenrep to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. On July 29, 2020, the Applicant agreed but proposed that healthcare settings be audited no later than 180 calendar days, which we agreed. This change in the time will allow the Agency to review audit methodology prior to the Applicant implementing the audits. Applicant has agreed to audit wholesalers-distributors no later than 90 calendar days after they become authorized to distribute Blenrep and annually thereafter. They will submit the audit and non-compliance protocols within 60 days from the date of approval.*

In addition, on July 27, 2020 we provided additional comments needed for the implementation system to be acceptable. In the section, "To support REMS Program operations, GlaxoSmithKline must," we have modified #1 and #7 for further clarification to support the REMS Program operations as follows:

> *1. Authorize dispensing for each patient based on receipt of the Patient Enrollment Form and Patient Status Form on the following schedule: Authorize the first dispensing upon receipt of the Patient Enrollment Form and Patient Status Form. If a completed Patient Enrollment Form and Patient Status Form are not received, the patient is not authorized to receive the drug. For*

subsequent dispensing, authorize dispensing based on receipt of the Patient Status Form. The authorization is valid for 14 calendar days from receipt of the Patient Status Form.

7. Ensure prescribers are able to use the Eye Care Professional Consult Request Form by fax and to adapt it as a template to use within healthcare information technology system software.

We have also inserted language to ensure that healthcare setting are able complete and submit the REMS Checklist online or by phone/fax as item #9 under "To support REMS Program operations, GlaxoSmithKline must," in the REMS document.

The Agency conveyed on July 27, 2020 that language regarding (b) (4) (b) (4) *in the REMS document to ensure that the REMS program requirements are carried out is covered by item #19-Establish a plan for addressing noncompliance, in the REMS Program operations of the REMS document. We informed the Applicant that the compliance assessment committee can be explained in the REMS Supporting Document.*

The Applicant agreed with these changes to the Implementation System; we have no further comments.

7.1.5 Timetable for Submission of Assessment for the REMS

The Applicant proposed to submit the REMS assessments (b) (4)

Reviewer Comments: *We did not agree with the Applicant's proposal of submittingREMS Assessments* (b) (4) *Due to the large number of the ocular toxicity reported in the clinical trial and to determine if there are issues with the initial implementation of this new REMS communicated with the Applicant on June 26, 2020, that they will be required to submit REMS assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS. The Applicant updated their timetable on July 10, 2020, to reflect this change.*

7.1.6 REMS Materials & Key Risk Messages

The Applicant included the following materials as part of the original submission of the REMS:

- Dear Healthcare Provider Letter (electronic and print): serves to inform the healthcare providers of the risk of ocular toxicity associated with Blenrep and provide information on the Blenrep REMS
- Dear Professional Society Letter (print): serves to inform the healthcare provider members of these societies of the risk of ocular toxicity associated with BLENREP and provide information on the Blenrep REMS.
- Program Overview: describes the requirements of the Blenrep REMS and responsibilities of prescribers and healthcare settings
  Prescriber Enrollment Form: serves to enroll the prescriber in the REMS and was discussed in section 7.1.3.
- Education Program for Prescribers: description of overview and clinical data of Blenrep, management of ocular adverse reactions and Blenrep REMS Goals and operations.

- Prescriber Knowledge Assessment: in order to enroll and become certified to prescribe Blenrep, healthcare providers must register on www.BLENREPREMS.com; review the drug's Prescribing Information, Program Overview, and Education Program for Prescribers; successfully complete the Knowledge Assessment with a 100% passing score and submit the Knowledge Assessment to the REMS Program, and subsequently complete the Prescriber Enrollment Form on the online portal or fax the completed form to the Blenrep REMS.
- Patient Guide: serves to inform the patient on the serious risks associated with Blenrep therapy, the REMS Program, and the requirement for monitoring via ophthalmic examinations (e.g., visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms.
- Patient Status Form: before each infusion, prescriber needs to assess patient's ocular health by consulting an eye care professional to complete the visual acuity and slit lamp examinations using the Eye Care Professional Consult Request Form, assess the patient's ophthalmic consult results for appropriateness of initiating treatment and document and submit to the Blenrep REMS using the Patient Status Form. Documentation and submission of Patient Status Form must be prior to each infusion.
- Patient Enrollment Form: completed by the prescriber and patient to enroll the patient into the REMS Program, and has patients attest to understanding the requirements under the REMS (i.e., reviewing the Patient Guide, being counseled, and completing the required monitoring).
- Healthcare Setting Enrollment Form: completed by the healthcare setting's authorized representative on behalf of the healthcare setting to enroll and certify into the REMS Program.
- Education Program for Health Care Settings: serves to provide a high-level summary of Blenrep REMS information including a Blenrep REMS overview, description of healthcare setting training, enrollment and setup.
- REMS Checklist: the content collected in the REMS checklist closes the loop on dispensing the drug and supports REMS operations and safety reporting activities.
- REMS Fact Sheet: serves to provide a high-level summary of Blenrep REMS information needed by healthcare providers including a Blenrep REMS overview, risk of ocular toxicity with Blenrep, how healthcare providers manage the risk, how to enroll, and reporting of adverse events.
- Website: an information source for stakeholders. It will allow healthcare providers, healthcare settings and patients to enroll and certify into the REMS program. Healthcare providers will be able to complete a Knowledge Assessment and also complete and submit a Patient Status Form. Healthcare settings will be able to obtain authorization to dispense online. The REMS appended materials, including a link to the Prescribing Information and Medication Guide will be accessible from the REMS website and available in a format that can be downloaded.

Reviewer's Comments: *We agree with the Applicant's proposed REMS materials, but also communicated on June 26, July 22, and July 28, 2020 that changes were needed to the proposed materials and one new material was necessary to support the various requirements of the REMS. The new material includes a Eye Care Professional Consult Request Form. The following additional materials were later developed by the Applicant, which will be part of REMS Supporting Document:*

- *REMS Online Portal Screenshots for Healthcare Settings*
- *REMS Online Portal Screenshots for Prescribers*

(b) (4)

The Applicant has incorporated all of the necessary changes, they are acceptable. The Applicant did not include key risk messages with their submissions of the REMS materials. See section 8 of this review for our proposed key risk messages.

7.1.7 REMS Assessment Plan

The Applicant included a REMS Assessment Plan for the proposed REMS in their Supporting Document in their initial submission on April 13, 2020. The initial proposed Assessment Plan included metrics about the approval and launch date of Blenrep, communication plan activities, a summary of REMS Call Center frequently asked questions, REMS compliance for prescribers, healthcare settings, and patients, and a healthcare provider knowledge survey.

Reviewer's Comments: *The Applicant's initial proposed Assessment Plan was lacking many metrics and we did not think it would not be sufficient to assess a REMS with ETASU. Furthermore, the format and content did not align with the Agency's draft guidance on REMS Assessment: Planning and Reporting. The Applicant was advised on June 26, 2020 to refer to this guidance for further guidance on developing and formatting an assessment plan, including developing a table that would outline how each objective of the goal is met. On July 10, 2020, the Applicant submitted a revised Assessment Plan, but the Assessment Plan was still missing several assessment categories. The Applicant then submitted the Assessment Plan Table on July 21, 2020. To support standardization of the format and content of a REMS Assessment Plan, the Agency provided a draft Assessment Plan to the Applicant on July 28, 2020 with further comments on July 31, 2020 and August 3, 2020. Further comments requested the Applicant to include the Assessment Plan Table accompanied by a discussion of how the REMS will be assessed and a brief section of the audit and non-compliance plans to the REMS Supporting Document. On August 5, 2020, the Applicant provided an updated Assessment Plan that was acceptable. The final and agreed upon REMS Assessment Plan is included in Section the Appendix 10.1 of this review.*

7.2 Other Proposed Risk Management Activities

In addition to the REMS materials, the Applicant has developed a (b) (4) (b) (4)

Reviewer's Comments: *This reviewer does not object to the Applicant developing (b) (4) materials (b) (4) that are outside of the REMS. The Office of Prescription Drug Labeling Promotion (OPDP) has advised that the Applicant's proposed non-REMS materials should be submitted to OPDP for review as they are not part of labeling or the REMS. We did not agree with including (b) (4) (b) (4) and on July 28, 2020 we conveyed to the Applicant that this should not be misconstrued as such. We do not oppose the Applicant (b) (4) however, the REMS should not be the mechanism to do this.*

In addition to the accelerated approval requirements, the Applicant will have the following Postmarketing Requirements (PMR)

- *A study to characterize the microcyst-like corneal deposits observed in patients with relapsed or refractory multiple myeloma treated with belantamab mafodotin, via superficial keratectomy assessments.*
- *Submit an integrated pooled analysis of adverse events, outcomes, management and discussion of potential mitigation strategies for ocular toxicity, from clinical trials to further evaluate the safety of the lyophilized presentation of belantamab mafodotin in patients with relapsed or refractory multiple myeloma.*
- *Conduct a randomized Phase 2 clinical trial to characterize the safety and efficacy of lower doses or alternative dosing regimens of single-agent belantamab mafodotin using the lyophilized presentation in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.*
- *Conduct a pharmacokinetic trial to determine the appropriate dose of belantamab mafodotin in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function that may inform labeling.*
- *Conduct a pharmacokinetic trial to determine the appropriate dose of belantamab mafodotin in patients with severe renal impairment and end-stage renal disease (ESRD) with or without dialysis compared to patients with normal renal function that may inform product labeling.*
- *Conduct a long-term storage stability assessment and submit the final report validating the bioanalytical measurement of cys-mcMMAF concentrations, previously submitted to this BLA, to establish the relationship between cys-mcMMAF exposure and safety events*

The Applicant will also be required to perform enhanced pharmacovigilance monitoring. For a period of 5 years from the U.S. approval date, they must submit all cases of changes in visual acuity to worse than 20/200, complete vision loss, corneal ulcers, and need for corneal transplant events reported with belantamab mafodotin as 15-day alert reports (as described under 21 CFR 600.80(c)(1)).

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for belantamab mafodotin-blmf, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

MM is the second most common hematological malignancy involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival. Regardless of substantial progress, MM remains a highly resistant disease given its propensity for clonal heterogeneity and its complex interaction with the surrounding bone marrow microenvironment. Treatment for these patients with RRMM is complex and there remains no consensus on a clear treatment algorithm. Despite significant therapeutic advances, MM remains incurable, and there is an unmet medical need for additional therapeutic options for patients who relapse and become refractory to available therapies.

Belantamab mafodotin-blmf is a B-cell maturation antigen (BCMA)-directed antibody-drug conjugate, with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma whose prior therapy included an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. Belantamab mafodotin-blmf is not currently approved in any jurisdiction.

Based on the efficacy and safety information, the clinical reviewers stated that belantamab mafodotin-blmf shows clinically meaningful benefit and, recommends approval of belantamab mafodotin-blmf for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.[30,31]

The most concerning risk associated with belantamab mafodotin-blmf is the risk of ocular toxicity, it was identified as a serious risk in clinical trials and was mitigated by conducting baseline and periodic ocular exams and dosage modifications or withholding treatment until the ocular toxicity improved. Although the ocular toxicities, including keratopathy, are a known class-effect associated with ADCs containing microtubule-inhibitor payloads, such as MMAF, the mechanism by which belantamab mafodotin-blmf causes ocular toxicity is not completely understood.[32,26] The toxicity observed with belantamab mafodotin-blmf is greater than that observed for other ADCs. The incidence and severity of keratopathy observed in the clinical trials was high (76%) and associated with clinically relevant decreases in visual acuity, including severe vision loss in some patients, and significant interference with patients' activities of daily living and impacts on driving and reading. Routine monitoring for the ocular toxicity, dose modifications, including dose interruption, dose reduction, and discontinuation of study treatment, are the primary mitigation strategy for the ocular toxicity observed with belantamab mafodotin-blmf in clinical trial. Despite evaluation of the lower 2.5 mg/kg starting dose of belantamab mafodotin, close monitoring with comprehensive ophthalmic exams at baseline and prior to each dose, and implementation of dose modifications, many patients had recurrent and/or unresolved events. Because many patients had significant keratopathy on ophthalmic exam in the absence of other ocular symptoms, there is also a concern that keratopathy could go undetected in the absence of close monitoring, potentially leading to serious sequelae, including the development of corneal ulcers.[26] Labeling will include a boxed warning for ocular toxicity and section 2 of the labeling will include recommendations for dosage modifications for patients who experience ocular toxicities. DRM and DHM2 have determined that if approved, labeling alone is not sufficient to mitigate these risks, a REMS is necessary to ensure the benefits of belantamab mafodotin-blmf outweigh its risk of ocular toxicity.

Belantamab mafodotin-blmf will be used in both inpatient and outpatient settings such as oncology infusion centers and prescribed by oncologist, hematologist, or other healthcare providers directly involved in the management of MM patients. It is expected that these prescribers would be familiar with the risks and management of thrombocytopenia, infusion-related reactions and embryo-fetal toxicity as these are not new or unusual adverse events associated with MM treatments. There is significant concern regarding the serious of the ocular toxicity and the management in the post marketing setting. Patients will need to have eye care exams performed prior to each dose, patients may initially be asymptomatic, most prescribers will not be familiar with the corneal adverse reactions and there will be a lack of familiarity with the recommendations for dosage modifications for corneal reactions in labeling that are based on both corneal examination findings and changes in BCVA. For these reasons the review team determined that labeling alone is not sufficient to mitigate the risk of ocular toxicity.

On May 12, 2020 this Application was discussed at the REMS Oversight Committee Meeting and on July 14, 2020 at the Oncologic Drugs Advisory Committee. Both concurred that a REMS with elements to assure safe use that included prescriber certification (ETASU A), healthcare setting certification (ETASU B), patient enrollment with documentation of safe use condition (ETASU D) and monitoring (ETASU E) are necessary to ensure the benefits of Blenrep outweigh the risk of ocular toxicity.

The REMS will also include a targeted communication plan to inform prescribers, healthcare settings and patients of the risks and that Blenrep is approved with a REMS that includes restricted distribution. It is the combination of the ETASU that comprise the REMS program and collectively support and ensure that the appropriate actions are taken by stakeholders to mitigate the risk of ocular toxicity. The details of this REMS was presented to the at the Oncology Center of Excellence Clinical Rounds on July 27, 2020, and discussed again with the ROC on August 4, 2020. There has been board support that a REMS that contains ETASU is necessary for belantamab mafodotin-blmf to ensure the benefits outweigh the risk of ocular toxicity.

We believe that the proposed REMS received on August 5, 2020, will support actions that will mitigate the risk of ocular toxicity by requiring that patients are required to conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms as per labeling.

Depending on the assessment findings, new safety information or other information, FDA may find it necessary to modify the REMS or consider other regulatory actions.

8.1 REMS MATERIALS AND KEY RISK MESSAGES

The following REMS materials will provide education and support the risks messages of the REMS:

- Dear Healthcare Provider Letter (electronic and print)
- Dear Professional Society Letter (print)
- Program Overview
- Prescriber Enrollment Form
- Education Program for Prescribers
- Prescriber Knowledge Assessment
- Eye Care Professional Consult Request Form
- Patient Guide
- Patient Status Form
- Patient Enrollment Form
- Healthcare Setting Enrollment Form
- Education Program for Health Care Settings
- RMES Checklist
- REMS Fact Sheet
- Website Screenshots

The key risk messages for healthcare providers are:

1. There is a risk of ocular toxicity associated with the use of BLENREP. Blenrep causes changes in the corneal epithelium resulting in changes in vision, including severe vision loss, and symptoms such as blurred vision and dry eyes.
2. Patients must have ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms.
3. Counsel patients using the Patient Guide on:
    - the risk of ocular toxicity

- the requirement for ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms.
- Enrollment into the Blenrep REMS before receiving Blenrep

4. Healthcare providers must complete Patient Status Form and submit to Blenrep REMS before patients can receive Blenrep.
5. Withhold Blenrep until improvement and resume at same or reduced dose, or permanently discontinue based on severity.
6. Blenrep must be infused in certified healthcare settings only after verification of ophthalmic examination.

The key risk messages for healthcare settings are:

1. There is a risk of ocular toxicity associated with the use of Blenrep.
2. Healthcare Settings must obtain authorization to administer each dose of Blenrep by contacting the Blenrep REMS to verify
   - the prescriber is certified in the BLENREP REMS,
   - the patient is enrolled in the BLENREP REMS and authorized to receive Blenrep for that dose
3. Complete the REMS Checklist and submit it to the Blenrep REMS within 5 business days of infusion.

The key risk messages for patients are:

1. The risk of eye problems is common with Blenrep and these can be serious.
2. Blenrep can cause changes to the surface of your eye that can lead to
   - dry eyes,
   - blurred vision,
   - worsening vision and
   - severe vision loss.
3. Tell your healthcare provider if you have any vision changes or eye problems during treatment with BLENREP.
4. Your healthcare provider will send you to see an eye specialist to check your eyes
   - before you start treatment,
   - prior to each dose, and
   - for worsening symptoms of eye problems
5. Even if your vision seems fine, you must get your eyes checked during treatment with Blenrep because some changes can happen without symptoms and may only be seen on an eye exam.

8.2 REMS Assessment Plan

Goal

The purpose of this REMS is to ensure that an ophthalmic examination is conducted prior to each dose. To be eligible for treatment, patients must be enrolled and authorized by a certified prescriber to receive treatment. Authorization of treatment includes patients obtaining an ophthalmic examination, prescribers reviewing the ophthalmic examination, and prescribers completing the Patient Status Form. Therefore, for the purpose of this REMS, having a completed Patient Status Form authorizing treatment

is a surrogate measure that patients have obtained an ophthalmic exam. To ensure these processes are undertaken by prescribers and patients, the REMS requires healthcare provider certification, patient enrollment, and healthcare setting certification. As a condition of certification or enrollment, each stakeholder attests to specific responsibilities and agrees to comply with the REMS requirements. The success of this REMS is contingent on the compliance of all three stakeholders to these processes, known as key performance indicators. Key performance indicators assist in determining whether the goal is achieved.

Key Performance Indicators

Healthcare provider certification

As a condition of certification, healthcare providers must be educated and trained, counsel patients on the risk, review ophthalmic examination results and, if appropriate, complete the Patient Status Form to allow patients to receive a dose of Blenrep. The number and percentage of completed Patient Status Forms authorizing treatment will provide data to inform objective 2a of the goal (ensuring healthcare providers are educated and adhered to submitting documentation that ophthalmic examinations at baseline and prior to each dose). Process metrics related to REMS operations (certification statistics, compliance data), knowledge evaluation (post-training knowledge assessment), and safe-use conditions (Patient Status Form) are necessary to assess the healthcare provider's compliance in enrolling the patient and authorizing the patient to receive a dose. For the purpose of this REMS, having a completed Prescriber Enrollment Form and an assessment of the post-training knowledge will provide data to inform objectives 1 and 2b of the goal (ensuring healthcare providers are educated on the risk and adhering to counseling patients).

Patient Enrollment

As a condition of enrollment, patients are required to be informed of the risk and agree to obtain ophthalmic examination prior to each dose. The Patient Enrollment Form is a critical form to capture that the counseling was completed. For the purpose of this REMS, a completed Patient Enrollment Form, is a surrogate measure of patients being informed. The number of patients enrolled as well as the number of patients receiving Blenrep prior to enrollment will provide data to inform objectives 2b (ensuring healthcare providers adhered to counseling) and 4 (ensuring patients are informed). Process metrics related to REMS operations (enrollment statistics, compliance data) and safe use conditions (Patient Status Form, REMS Verification, REMS Checklist) are necessary to assess if patients are being informed and enrolled and agree to obtain an ophthalmic examination prior to each dose.

Healthcare setting certification

As a condition of certification, the healthcare setting must verify that the healthcare provider is certified, and the patient is eligible to receive Blenrep prior to dispensing Blenrep. This verification serves as the last safety check before Blenrep is dispensed. Processes such as the REMS Verification and REMS Checklist were established to ensure that these steps will be taken. Data on the REMS Verification and REMS Checklist as well as data on healthcare setting compliance will inform objective 3a (ensuring safe use of Blenrep by ensuring Blenrep is infused in certified healthcare settings only after verification of ophthalmic examination). Process metrics related to REMS operation (healthcare setting certification statistic and compliance data) and safe-use conditions (REMS Verification and REMS Checklist) are

necessary to assess the healthcare setting's compliance in verifying that the healthcare provider is certified and only eligible patients will receive Blenrep.

Target

Target is the level of benchmark to achieve key performance indicators. The conditions and processes described above are in place to ultimately ensure that only eligible treatments are appropriately dispensed. The target to measure the key performance indicators is the percentage of eligible treatments dispensed among all treatments dispensed, including eligible and non-eligible treatments. Due to the REMS conditions and processes and restricted distribution of Blenrep, the percentage of eligible treatments dispensed is expected to be high (at least 90% during initial implementation). The Agency recognizes that for the first few years of the REMS, the REMS is being implemented, communication plan activities are ongoing to alert stakeholders of the new drug and REMS, and stakeholders will need sufficient time to be trained and educated. The Agency will closely monitor the REMS processes for the first four years to ensure that conditions and processes are met. Once the REMS is well-established, it is expected that this 90% of eligible treatments dispensed (i.e. patient is enrolled and authorized to receive treatment via the Patient Status Inform which indicate that an ophthalmic exam was conducted) will improve as the Applicant and stakeholders gain more experience with the REMS.

Secondary Measures

Other secondary measures include Blenrep utilization, appropriateness of treatment modification, knowledge sustainability, and measures of burden or access problems. These secondary measures provide context and inform the overall function of the REMS. Data collected through these measures can assist in determining the next course of regulatory actions for the REMS, such as REMS modification.

Blenrep Utilization

These metrics provide context for the use of Blenrep. In clinical trials, Blenrep was mostly dispensed in academic or tertiary centers. The setting of use in the post marketed setting is likely to be shifted towards more community settings. Furthermore, in DREAMM-2, approximately 84% of patients were between 18 to <75 years of age and 15% were over 75 years of age. Monitoring how Blenrep is used in a real-world setting can help support the REMS in understanding the benefit risk assessment over time.

Treatment Modification

An assumption of the REMS is that prescribers are educated and will modify treatment accordingly per the Prescribing Information. For Grade 2 or higher corneal adverse events, prescribers are instructed to hold the dose until improvements are noted. Depending on the grade of the corneal adverse events, treatment may be restarted at the same dose or a reduced dose. An assessment of treatment modification will assess whether treatment is held in patients who develop a Grade 2 or higher corneal adverse event. This data is collected through the Patient Status Form and will support the REMS in ensuring that only eligible patients receive Blenrep.

Knowledge Sustainability

A healthcare provider knowledge survey will be conducted every other year starting with the Year 2 assessment report. The survey is intended to start at the Year 2 assessment report to allow time for the REMS to be implemented, communication activities to be undertaken, and for prescribers to be educated and experienced with using Blenrep. It is to be conducted every other year to allow appropriate time for recruitment and changes to be incorporated (if applicable) in order to have a rigorous study with robust results. Survey data can add value in assessing whether knowledge is sustained and whether healthcare providers are counseling patients which is a key requirement in this REMS. It can also measure the extent of awareness and usage of REMS materials as well as attitudes and behavior towards the REMS. A patient survey was deemed not necessary since patients will be informed of the risk through the prescriber and through regular ophthalmic examinations. Should there be non-compliance to the REMS requirements and/or an increase in the reporting of corneal adverse events, the Agency may ask the Applicant to conduct further studies (e.g. patient survey or qualitative studies) to further investigate if patients are not appropriately informed. The survey data will support the REMS in ensuring that healthcare providers are educated and counseling patients. The Applicant agrees to submit the survey methodology protocol within 60 days from date of approval.

Burden and Access

Multiple data sources are used to measure burden and access problems. The survey may contain specific questions to evaluate respondents' attitudes on potential burden associated with REMS requirements. The time between patient enrollment and date of the first ophthalmic examination may be evaluated to determine challenges of finding an eye care professional. A summary of calls to the REMS Call Center and a summary of reasons for stakeholders who are unable to become certified or enrolled, are other data sources to measure any unintended consequences that could affect patient access or potential burden to the healthcare system related to program operations. Collectively, this data on burden and access can support reassessment of the requirements and/or their implementation and assist in minimizing these effects. This analysis may help inform any necessary modification to the REMS.

As described above in Section 7.1.3, the prescriber is expected to transcribe the ophthalmic examination results from the Eye Care Professional Consult Request Form to the Patient Status Form. A one-time qualitative study focusing on administrative burden and prescriber's attitudes and beliefs around this requirement is to be conducted and results will be included in the Year 1 assessment report. This information is to assess unnecessary burden or inefficiencies in the program. This requirement will be monitored and revisited during the Year 1 assessment report. The Applicant agrees to submit the qualitative study protocol within 60 days from date of approval.

9 Conclusion & Recommendations

The severity of the risk of ocular toxicity associated with belantamab mafodotin-blmf is such that it is necessary for prescribers to understand the risk, the importance of monitoring for it, the need to take appropriate actions when ocular toxicity is detected, and the need to counsel patients on the risk prior to prescribing belantamab mafodotin-blmf. Based on the severity of ocular toxicity, that occur with chronic belantamab mafodotin-blmf therapy, we have determined that a REMS consisting of a communication plan, prescriber certification, healthcare setting certification, patient enrollment with documentation of safe use condition and monitoring is necessary to ensure that the benefits outweigh the risks.

The REMS submitted by the Applicant on August 5, 2020 is acceptable for approval.

10 Appendices

10.1 BLENREP REMS ASSESSMENT PLAN

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. REMS communication plan activities (6-month, 1-year, and 2-year assessments only)

    a. Sources for the distribution lists for healthcare providers
    b. Number of healthcare providers targeted
    c. Number of healthcare professional societies targeted, and which healthcare professional societies distributed the REMS letter for distribution to their respective members.
    d. The number of REMS materials packets sent by date, attempt, and method of distribution
    e. The number and percentage of emails successfully delivered, opened, and unopened
    f. The number and percentage of mails successfully delivered and returned as undeliverable
    g. The number of REMS fact sheets distributed to targeted healthcare providers during the 12 months after approval of the REMS.
    h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed.

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)

    a. Date of first commercial distribution of Blenrep
    b. Date when the REMS website became live and fully operational
    c. Date when the REMS portal became live and fully operational
    d. Date when the REMS Call Center was established and fully operational

3. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)

    a. Healthcare provider certification

        i. Number of newly certified and active healthcare providers (i.e. who have prescribed Blenrep at least once during the reporting period) stratified by

provider type (e.g. Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (i.e. oncology, other) and geographic region (as defined by US Census).

ii. Number of healthcare providers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

b. Healthcare setting certification

i. Number of newly certified and active healthcare settings (i.e. have dispensed Blenrep at least once during the reporting period) stratified by healthcare setting type (i.e. infusion center, group practice, independent practice, outpatient clinic, hospital, other) and geographic region (as defined by US Census)

ii. Number of healthcare setting that were unable to become certified, accompanied by a summary of the reasons they were unable to become certified

c. Patient enrollment

i. Number of newly enrolled and active patients (i.e., have received Blenrep at least once during the reporting period) stratified by age in years (mean, standard deviation, median, range), age group (<18, 18 to 64, 65 to 74, ≥75), gender and geographic region (as defined by US Census).

ii. Number of patients who were unable to become enrolled, accompanied by a summary of the reasons they were unable to be enrolled

d. Wholesalers/Distributor enrollment

i. The number of newly enrolled and active wholesaler/distributors (i.e. have shipped Blenrep at least once during the reporting period)

4. Blenrep Utilization Data (provide for each reporting period and cumulatively)

a. Number and percentage of unique patients who received Blenrep, stratified by type of healthcare setting.
b. Number and percentage of healthcare providers who wrote Blenrep prescriptions that were dispensed, stratified by medical specialty (e.g. oncology, other) and provider type
c. Number and percentage of Blenrep shipments sent to healthcare settings stratified by type of healthcare setting.

5. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)

a. REMS Website
   i. The number of visits and unique visits to the REMS website
   ii. The number of REMS materials downloaded for each material

b. REMS Call Center

i. The number of calls received by the REMS call center, stratified by stakeholder type (patient, healthcare provider, healthcare setting, other), accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls).
ii. The number of REMS Program issues/complaints reported to the REMS call center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls) and the resolution (if applicable)
iii. A summary and analysis of calls that may indicate an issue with patient access, or burden on the healthcare delivery system
iv. A summary of corrective actions resulting from issues identified through the REMS Call Center
v. The number of REMS materials requested through the REMS call center

6. REMS Compliance (provide for each reporting period and cumulatively)

a. Audits: Summary of audit activities including but not limited to:
   i. A copy of the audit plan for each audited stakeholder.
   ii. The number of audits expected, and the number of audits performed
   iii. The number and type of major and critical deficiencies noted
   iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required to address the deficiencies, including the status (e.g., completed, not completed, in progress).
   v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
   vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements

b. A summary report of non-compliance, associated CAPA plans, and the status of CAPA plans including but not limited to:
   i. A copy of the Non-Compliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
   ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

      1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

      2. The source of the noncompliance data

      3. The results of root cause analysis

      4. What action(s) were taken in response.

c. Healthcare provider non-compliance

i. Number and percentage of all dispenses reported to Blenrep REMS via the REMS Checklist that were written by non-certified healthcare providers among all dispenses of Blenrep
    1. For all dispenses of Blenrep that were prescribed by a non-certified healthcare provider, a summary report including whether an ophthalmic exam was obtained and whether the healthcare provider later became certified, and if so, the time elapsed between dispenses and healthcare provider certification, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

ii. Number of healthcare providers who became decertified as a result of non-compliance, accompanied by a summary of reasons for decertification

d. Healthcare setting non-compliance

i. Number and percentage of all dispenses reported to the Blenrep REMS via the REMS Checklist by non-certified healthcare setting among all dispenses of Blenrep.
    1. For all dispenses of Blenrep by non-certified healthcare setting, a summary report including whether an ophthalmic exam was obtained and whether the healthcare setting later became certified, and if so, the time elapsed between dispenses and healthcare setting certification, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

ii. Number and percentage of all dispenses reported to the Blenrep REMS via the REMS Checklist to non-enrolled patients among all dispenses of first dose of Blenrep
    1. For all dispenses of Blenrep to non-enrolled patients, a summary report including whether an ophthalmic exam was obtained and whether the patients later became enrolled, and if so, the time elapsed between dispenses and patient enrollment, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

iii. Number and percentage of all dispenses reported to the Blenrep REMS via the REMS Checklist to non-eligible patients among all dispenses of subsequent doses of Blenrep.

    1. For all dispenses of Blenrep to non-eligible patients, a summary report including whether an ophthalmic exam was obtained, if a Patient Status Form was received, and if so, the time elapsed between dispenses and receipt of Patient Status Form, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

iv. Number and percentage of all dispenses reported to the Blenrep REMS via the REMS Checklist that were written by non-certified healthcare providers for non-enrolled patients at non-certified healthcare setting among all dispenses of Blenrep

1. For all dispenses of Blenrep that were written by non-certified healthcare provider for non-enrolled patients at non-certified healthcare setting, a summary report including whether an ophthalmic exam was obtained, whether patients later became enrolled, whether healthcare provider and healthcare setting later became certified, and if so, the time elapsed between dispenses and patient enrollment and prescriber and healthcare setting certification, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

v. Number and percentage of all dispenses reported to the Blenrep REMS via the REMS Checklist that bypassed the REMS verification process among all dispenses of Blenrep

1. For all dispenses of Blenrep that bypassed the REMS verification process, a summary report including whether an ophthalmic exam was obtained, healthcare provider certification status, patient enrollment status, and whether a current Patient Status Form is received, and trends related to repeat occurrences of noncompliance for each of these events will be provided.

vi. The number of healthcare setting that became decertified as a result of non-compliance, accompanied by a summary of reasons for decertification

e. Wholesaler/distributor non-compliance

i. Number and percentage of shipments distributed by non-authorized wholesaler or distributor
ii. Number and percentage of Blenrep shipments distributed to non-certified healthcare settings

Safe Use Behaviors

7. Patient Status Forms (provide for each reporting period and cumulatively)

a. Number and percentage of patients for whom ≥Grade 2 corneal adverse reactions were not reported, stratified by dose cycle (e.g. 1st, 2nd, 3rd, or 4th dose). Provide a summary and data in a tabular format.
b. Number and percentage of patients who did not have a Patient Status Form submitted prior to each infusion among all dispenses reported to the Blenrep REMS via the REMS

Checklist stratified by dose cycle (e.g. 1st, 2nd, 3rd, 4th dose). Provide a summary and tabular format.

i. For all patients who did not have a Patient Status Form submitted prior to each dose, a summary of the reasons ophthalmic exam was not performed, and the source of reason information (e.g., healthcare provider or patient)

c. Number and percentage of patients who did not receive an eye exam prior to each dose.
d. Time between enrollment and date of first eye exam.
e. Number of patients who experienced a treatment interruption, and resumed treatment including the duration of treatment interruption and reason for treatment interruption due to ocular events.
f. Number and percentage of patients who were unable to be dosed within the 14-day window and needed to repeat an ophthalmic exam after the 14-day window expired.
g. Number of patients who developed a ≥Grade 2 corneal adverse reaction and had the last infusion withheld (i.e. patient did not receive Blenrep) among all active patients (have received Blenrep at least once during the reporting period) stratified by each dose cycle (1st, 2nd, 3rd, 4th dose). Provide a summary and data in a tabular format.
h. Number and percentage of Patient Status Forms submitted where the prescriber attested to reviewing the ophthalmic exam and authorizing treatment among all Patient Status Forms submitted

8. REMS Verification and Checklist

a. Number of all dispenses reported to the Blenrep REMS via the REMS Checklist.
b. Number and percentage of eligible treatments dispensed among all treatment dispenses reported to the Blenrep REMS via the REMS Checklist (eligible and non-eligible). For non-eligible treatments, provide the source of information (e.g. REMS Call Center, healthcare provider, healthcare setting or patient, etc.)
c. Number and percentage of patients who had a REMS checklist submitted beyond the targeted timeframe of 5 days among all patients who were dispensed Blenrep.
d. Number and percentage of times when the verification results indicate "DO NOT INFUSE." Include a summary of the reasons why patient is unable to receive the dose (e.g. provider is not certified, patient is not enrolled, no Patient Status Form)

9. Prescriber Treatment Modification Assessment (provide for each reporting period and cumulatively)

a. Number and percentage of healthcare providers who documented that treatment was modified on the Patient Status Form for patients with ≥Grade 2 corneal adverse events. Include the number and percentage of patients who had a Patient Status Form documenting the prescriber recommending dose modification. Provide a summary and data in a tabular format.
b. Number and percentage of healthcare providers who did not modify treatment accordingly per the Prescribing Information for patients with ≥Grade 2 corneal adverse events. Provide a summary and data in a tabular format.
    i. For patients with Grade 2 (moderate superficial keratopathy or decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200), a

summary including whether Blenrep was withheld, if ophthalmic exam findings improved to Grade 1 or better, and whether treatment was restarted and at what dose.

ii. For patients with Grade 3 (severe superficial keratopathy or decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200), a summary including whether Blenrep was withheld, if ophthalmic exam findings improved to Grade 1 or better, and whether treatment was restarted at a reduced dose.

iii. For patients with Grade 4 (corneal epithelial defect or Snellen Visual Acuity worse than 20/200), a summary including whether patients restarted treatment and at what dose.

10. Prescriber Burden Assessment (1-year assessment only)

a. A qualitative study to assess administrative burden and prescribers' attitudes and beliefs around the requirement for transcribing the ophthalmic examination findings from the Eye Care Professional Consult Request Form to the Patient Status Form.

Knowledge

11. Knowledge Assessments (provide for each reporting period and cumulatively)

a. The number of completed post-training knowledge assessments for healthcare providers, including the method of completion and the number of attempts to complete.
b. A summary of the most frequently missed knowledge assessment questions.
c. A summary of potential comprehension or perception issues identified with the knowledge assessment.

12. Stakeholder Survey (beginning with the 2-year assessment report and every other year thereafter)

a. Healthcare provider survey to assess if healthcare providers are educated on the following:
    i. The risk of ocular toxicity associated with the use of Blenrep
    ii. The need to submit documentation that ophthalmic exams are being done at baseline and prior to each dose to identity ocular toxicity
    iii. The need to counsel patients on the risk of ocular toxicity and the requirement for monitoring via ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms as described in the Prescribing Information.

Health Outcomes and/or Surrogates of Health Outcomes

13. Safety Surveillance (provide for each reporting period and cumulatively)

a. Known, or suspected ≥Grade 2 corneal adverse reactions are to be reported regardless of outcome. Provide an overall analysis and discussion of all cases identified from all sources (i-vii):

i. Patient Enrollment Form
ii. Patient Status Form
iii. REMS Checklist
iv. Spontaneous adverse event reports
v. Literature searches
vi. Social media
vii. Call center

b. The overall analysis and discussion on ≥Grade 2 corneal adverse reactions including but not limited to:
    i. For each patient with a ≥Grade 2 corneal adverse reaction, a summary including whether an ophthalmic exam was conducted prior to each dose, progression of keratopathy or changes in visual acuity at each ophthalmic exam prior to each dose, appropriateness of treatment modification, whether there were improvements to a Grade 1 or better if treatment was restarted and if restarted, whether the dose was restarted at the same or reduced dose. Provide a summary and data in a tabular format.
    ii. Patient age (Median, Range)
    iii. Patient age group (<18, 18 to 64, 65 to 74, ≥75)
    iv. Total Dose (Mean, Range)
    v. Dose per cycle (mg/dose)
    vi. Cumulative Time to Event Analysis, stratified by patient age group, Total Dose (Mean, Range)
c. For Grade 2, 3 and 4 corneal adverse reaction, stratified by age group and dosing, which may include:
    i. Number of cases requiring hospitalization (non-stratified)
    ii. Number of cases leading to dose reduction
    iii. Number of cases leading to dose interruption/delay
    iv. Number of cases that were withheld for more than 6 months
d. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

14. The requirements for assessments of an approved REMS under section 505- 1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified

11 References

[1] Draft Prescribing Information for belantamab mafodotin-xxxx as currently edited by the FDA, last updated August 4, 2020.

[2] The Oncologic Drugs Advisory Committee (ODAC). July 14, 2020; https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-july-14-2020-meeting-oncologic-drugs-advisory-committee

[3] Marino S, Petrusca DN, Roodman GD. Therapeutic targets in myeloma bone disease. *Br J Pharmacol.* 2019.

[4] Smith L, McCourt O, Henrich M, et al. Multiple myeloma and physical activity: a scoping review. *BMJ Open.* 2015;5(11):e009576.

[5] National Institutes of Health (NIH). The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed July 19, 2020.

[6] Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma--does it matter? *Haematologica.* 2015;100(6):704-705.

[7] Zweegman S, Engelhardt M, Larocca A. Elderly patients with multiple myeloma: towards a frailty approach? *Curr Opin Oncol.* 2017;29(5):315-321.

[8] Dolloff NG, Talamo G. Targeted therapy of multiple myeloma. *Adv Exp Med Biol.* 2013;779:197-221.

[9] Majithia N, Vincent Rajkumar S, Lacy MQ, et al. Outcomes of primary refractory multiple myeloma and the impact of novel therapies. *Am J Hematol.* 2015;90(11):981-985.

[10] Thalomid. Prescribing Information (last updated 06/2019).

[11] Revlimid. Prescribing Information (last updated 10/2019).

[12] Pomalyst. Prescribing Information (last updated 10/2019).

[13] Velcade. Prescribing Information (last updated 04/2019).

[14] Kyprolis. Prescribing Information (last updated 10/2019).

[15] Ninlaro. Prescribing Information (last updated 11/2016).

[16] Darzalex. Prescribing Information (last updated 09/2019).

[17] Empliciti. Prescribing Information (last updated 10/2019).

[18] NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma. Version 3 2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. 2019 June 19; accesses: July 19, 2020.

[19] Chantrain CF, Feron O, Marbaix E, DeClerck YA. Bone marrow microenvironment and tumor progression. *Cancer Microenviron.* 2008;1(1):23-35.

[20] Mohty B, El-Cheikh J, Yakoub-Agha I, Avet-Loiseau H, Moreau P, Mohty M. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and 'retreatment' approaches in the era of novel agents. *Leukemia.* 2012;26(1):73-85.

[21] Korneev KV, Atretkhany KN, Drutskaya MS, Grivennikov SI, Kuprash DV, Nedospasov SA. TLR-signaling and proinflammatory cytokines as drivers of tumorigenesis. *Cytokine.* 2017;89:127-135.

[22] Varga C, Laubach JP, Anderson KC, Richardson PG. Investigational agents in immunotherapy: a new horizon for the treatment of multiple myeloma. *British journal of haematology.* 2018;181(4):433-446.

[23] Mikhael J. Treatment Options for Triple-class Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk.* 2020;20(1):1-7.

[24] Xpovio. Prescribing Information (last updated 6/2020).

[25] Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med.* 2019;381(8):727-738.

[26] Combined FDA and Applicant ODAC Briefing Document, The Oncologic Drugs Advisory Committee (ODAC). July 14, 2020; https://www.fda.gov/media/139926/download

[27] GlaxoSmithKline Intellectual Property Development Ltd. Clinical Protocol for belantamab mafodotin-blmf, dated November 26, 2019.

[28] GlaxoSmithKline Intellectual Property Development Ltd. Clinical Study Report for belantamab mafodotin-blmf, dated November 26, 2019.

[29] GlaxoSmithKline Intellectual Property Development Ltd. Summary of Clinical Safety for belantamab mafodotin-blmf, dated December 5, 2019.

[30] Baines A and Ershler R. Clinical Review Presentation. Mid-Cycle Meeting, dated February 3, 2020

[31] BLA Multi-disciplinary Review and Evaluation (Draft) for BLA 761158 belantamab mafodotin-blmf, dated August 4, 2020.

[32] Zhao H, Atkinson J, Gulesserian S, et al. Modulation of Macropinocytosis-Mediated Internalization Decreases Ocular Toxicity of Antibody-Drug Conjugates. *Cancer Res.* 2018;78(8):2115-2126.

144 Pages of Draft REMS have been Withheld in Full as b4 (CCI/TS) immeidately following this page

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Carolyn Tieu, Pharm.D., MPH, Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 31, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Blenrep (belantamab mafodotin-blmf). On December 5, 2019, GlaxoSmithKline Intellectual Property Development Ltd. (GSK) submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) This application is under review in the Division of Hematology Malignancies 2 (DHM2).

The Applicant's proposed REMS submitted on May 7 (Global Submit;GS), July 7 (email), July 10 (GS), July 17 (email), July 21 (GS) and July 24 (email), July 27 (docuBridge) and July 29 (email), 2020, are the subject of this review. Their proposed REMS consist of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Materials Reviewed

General comments on the Applicant's REMS document, REMS Supporting Document and REMS materials were provided on June 26, 2020. On July 10, 2020, the Applicant provided responses to the Agency's comments. FDA provided comments on July 22 and July 28, 2020, on attestations for the prescriber, healthcare setting and patient enrollment forms, which have been reviewed by the Offices of Regulatory Policy (ORP) and Chief Counsel (OCC). In addition to the review by the DRM, the REMS Document has been reviewed by the OCC. The revisions to this document include OCC's comments.

The following materials have been reviewed and comments on these materials are appended to this review:

- REMS Document
- REMS Supporting Document
- Patient Status Form
- REMS Checklist
- Eye Care Professional Consult Request Form
- Program Overview
- Education Program for Prescribers
- Patient Guide
- REMS Fact Sheet
- Education Program for Healthcare Settings
- REMS Website (public facing)
- REMS Letter for Healthcare Providers (print and email)
- REMS Letter for Professional Societies

Materials in Supporting Document

- REMS Prescriber Portal screenshots
- REMS Healthcare Setting Portal screenshots
- (b) (4)

3 Comments to the Applicant

The Agency has reviewed the proposed REMS Document and REMS Supporting Document, submitted on May 7 (Global Submit; GS), July 7 (email), July 10 (GS), July 17 (email), July 21 (GS) and July 24 (email), July 27 (docuBridge) and July 29 (email), 2020. Please see the summary of comments below, as well as the redlined changes and specific comments provided in each document attached.

Please see the summary of comments below for REMS Document and appended REMS materials, as well as the redlined changes and specific comments provided in each document attached.

General Comment

We remind you that REMS materials must align with the Prescribing Information.

We have no additional comments on the following materials: REMS Checklist, Prescriber Knowledge Assessment, Education Program for Healthcare Settings.

All materials submitted must be included in either the REMS Document or the Supporting Document. Include the following materials as part of the Supporting Document: REMS Prescriber Portal screenshots, REMS Healthcare Setting Portal screenshots, (b) (4)

I. REMS Document

Since inclusion of (b) (4) in the goal, we determined that the statement this text is not necessary and does not need to be included in the goals. Removal of this text from the goal does not change any of the program requirements.

The Agency acknowledges your request for Agency's feedback within 30 days of receipt of the audit protocol. In order to allow for sufficient time for review, the Agency requests that you submit the audit and non-compliance protocols within 60 days from the date of the approval. The Agency will provide feedback within 60 days of receipt of the protocols.

II. REMS Supporting Document

Align the REMS Supporting Document with the REMS Document and label.

III. REMS Materials

Patient Status Form:

We do not agree with your proposed [redacted]

The edits from the introduction section up to the assessment section are acceptable. Remove the [redacted] within the [redacted] section of the form. "Normal" must be defined on this form. Normal criteria can be presented either as part of the Dosage Modifications for Corneal Adverse Reactions per the KVA Scale chart or described as part of Question # 3 in the ophthalmic assessment.

You may maintain the information regarding a prescriber or prescriber delegate. You may include a statement instructing prescribers to notify the BLENREP REMS if an enrolled patient who has received BLENREP is no longer under the prescriber's care or has discontinued treatment.

Eye Care Professional Consult Request Form:

We accepted many of your revisions on this form. However, there needs to be a summary finding for the ophthalmologist to check on the form, so the oncologist can quickly find the results and then determine any dose or treatment modifications. Maintain the checkbox and grade of normal in the corneal adverse reactions for KVA Scale chart.

Program Overview:

See edits to align with REMS Document.

Education Program for Prescribers:

The data presentation must reflect the Prescribing Information. We have recommended deletion of slides that are not relevant to include as part of the REMS. Clinical presentation of data must also include the 2.5 mg/kg dose on DREAMM-2 study within the slides.

Patient Guide:

We note your agreement to remove [redacted]
Remove [redacted] as it is not a part of the REMS program. See edits on Patient Guide.

REMS Website:

See edits to align website with Prescribing Information and REMS Document.

REMS Letter for Healthcare Providers:

See edits on to better align with Prescribing Information. Apply to both print and email versions of Letters.

REMS Factsheet:

See edits to align Factsheet with Prescribing Information and REMS Document.

REMS Letter for Professional Societies:

See edits to better align with Prescribing Information

Materials in the Supporting Document

REMS Prescriber Portal screenshots:

We acknowledge that slide content will be updated with final versions of materials. See edits on screenshots.

REMS Healthcare Setting Portal screenshots:

We have provided typographical edits. We acknowledge that slide content will be updated with final versions of materials. See edits on screenshots.

(b) (4)

IV. REMS Assessment Plan

See the attached REMS Supporting Document for edits and comments regarding the draft Assessment Plan. The Assessment Plan is not considered final and undergoing discussions at the Agency.

Update the proposed REMS Assessment Plan (b) (4) include a summary of how you will be using the assessment categories and metrics to inform the goal and objectives as well as setting performance thresholds that would indicate that the REMS is functioning optimally.

162 Pages of Draft REMS have been Withheld in Full as b4 (CCI/TS) immediately followring this page

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/s/

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Carolyn Tieu, Pharm.D., MPH, Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 28, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

1 Introduction

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The Applicant's proposed REMS submitted on July 7 (email), July 10 (Global Submit; GS), July 17 (email), July 21 (GS) and July 24 (email), 2020 are the subject of this review. Their proposed REMS consists of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Materials Reviewed

General comments on the Applicant's REMS materials were provided on June 26, 2020. On July 10, 2020, the Applicant provided responses to the Agency's comments. FDA provided comments on July 22, 2020, on attestations for the prescriber, healthcare setting and patient enrollment forms, which have been reviewed by the Offices of Regulatory Policy (ORP) and Chief Counsel (OCC). We also provided comments on the Eye Care Professional Consult Request Form, Patient Status Form, REMS Checklist, Education Program for Prescribers and Prescriber Knowledge Assessment. In addition to the review by the DRM, the REMS Document has been reviewed by the OCC. The revisions to this document include OCC's comments, which was provided to the Applicant on July 27, 2020.

The following materials have been reviewed and comments on these materials are appended to this review:

- Attestations for the prescriber, healthcare setting and patient enrollment forms
- Prescriber Enrollment Form
- Patient Enrollment Form
- Healthcare Setting Enrollment Form

3 Comments to the Applicant

The Agency has reviewed the proposed Prescriber Enrollment Form, Patient Enrollment Form, and Healthcare Setting Enrollment Form submitted on July 10, 2020 and the proposed revisions to the attestations in the Prescriber, Healthcare Setting, and Patient Enrollment forms submitted on July 24,

2020. Note that the attestations have been revised, these should be used as the attestations in your Prescriber, Healthcare Setting, and Patient Enrollment forms.

Please see the summary of comments below for attestations in the Prescriber, Healthcare Setting, and Patient Enrollment forms, Patient Enrollment Form and REMS Assessment Plan, as well as the redlined changes and specific comments provided in each document attached. Additional comments on other REMS materials will be forthcoming later this week. Please wait for all of FDAs comments on materials before responding with any submissions either by email or through Gateway. Once all FDA comments have been sent on all REMS materials, GSK can submit one complete submission containing all REMS materials.

REMS Materials

Attestations

Please see the attestations with our comments. We do not agree (b) (4) as this is not a requirement of the BLENREP REMS. However, we can include a statement similar to this on the Patient Status Form as a reminder for prescribers. Additional comments on the Patient Status Form are forthcoming.

Update all enrollment forms with revised attestation language.

Patient Enrollment Form

We do not agree (b) (4)

Assessment Plan

The REMS assessment plan is not finalized and is still under discussion within the Agency. See below for a draft REMS assessment plan. The Agency reserves the right to require additional studies (e.g. additional audits, patient survey, patient focus group, healthcare provider focus group) after REMS implementation or if the Agency identifies insufficient compliance with the REMS requirements.

Update the REMS supporting document with the draft assessment plan.

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. REMS communication plan activities (6-month, 1-year, and 2-year assessments only)
    a. Sources for the distribution lists for healthcare providers
    b. Number of healthcare providers targeted

c. Number of healthcare professional societies targeted, and which healthcare professional societies distributed the REMS letter for distribution to their respective members.
d. The number of REMS materials packets sent by date, attempt, and method of distribution
e. The number and percentage of emails successfully delivered, opened, and unopened
f. The number and percentage of mails successfully delivered and returned as undeliverable
g. The number of REMS fact sheets distributed to targeted healthcare providers during the 12 months after approval of the REMS.
h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed.

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)
    a. Date of first commercial distribution of Blenrep
    b. Date when the REMS website became live and fully operational
    c. Date when the REMS portal became live and fully operational
    d. Date when the REMS Call Center was established and fully operational

3. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)

    a. Healthcare provider certification

        i. Number of newly certified and active healthcare providers (i.e. who have prescribed Blenrep at least once during the reporting period) stratified by provider type (e.g. Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (e.g. oncology, other) and geographic region (as defined by US Census).
        ii. Number of healthcare providers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

    b. Healthcare setting certification

        i. Number of newly certified and active healthcare setting (i.e. have dispensed Blenrep at least once during the reporting period) stratified by healthcare setting type (i.e. infusion center, group practice, independent practice, outpatient clinic, hospital, other) and geographic region (as defined by US Census)
        ii. Number of healthcare setting that were unable to become certified, accompanied by a summary of the reasons they were unable to become certified

    c. Patient enrollment
        i. Number of newly enrolled and active patients (i.e., have received Blenrep at least once during the reporting period) stratified by age in years (mean,

standard deviation, median, range), age group (<18, 18 to 64, 65 to 74, ≥75), gender and geographic region (as defined by US Census).

ii. Number of patients who were unable to become enrolled, accompanied by a summary of the reasons they were unable to be enrolled

d. Wholesalers/Distributor enrollment

i. The number of newly enrolled and active wholesaler/distributors (i.e. have shipped Blenrep at least once during the reporting period)

4. Blenrep Utilization Data (provide for each reporting period and cumulatively)

a. Number and percentage of unique patients who received Blenrep, stratified by type of healthcare setting.
b. Number and percentage of healthcare providers who wrote Blenrep prescriptions that were dispensed, stratified by medical specialty (e.g. oncology, other) and provider type
c. Number and percentage of Blenrep shipments sent to healthcare settings stratified by type of healthcare setting.

5. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)

a. REMS Website

i. The number of visits and unique visits to the REMS website
ii. The number of REMS materials downloaded and printed for each material

b. REMS Call Center

i. The number of calls received by the REMS call center, stratified by stakeholder type (patient, healthcare provider, healthcare setting, other), accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls).
ii. The number of issues/complaints reported to the REMS call center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls) and the resolution (if applicable)
iii. A summary and analysis of calls that may indicate an issue with patient access, or burden on the healthcare delivery system
iv. A summary and analysis of calls that may indicate (b) (4)
v. A summary of corrective actions resulting from issues identified
vi. The number of REMS materials requested through the REMS call center

6. REMS Compliance (provide for each reporting period and cumulatively)

a. Audits: Summary of audit activities including but not limited to:

i. A copy of the audit plan for each audited stakeholder.
ii. The number of audits expected, and the number of audits performed

iii. The number and type of deficiencies noted
iv. For those with deficiencies noted, report the status (e.g., completed, not completed, in progress) and corrective and preventative action (CAPA) required to address the deficiencies.
v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
vi. (b) (4)
vii.
viii.
ix. A summary report of any resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements

b. A summary report of non-compliance, associated CAPA plans, and the status of CAPA plans including but not limited to:

i. A copy of the Non-Compliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
    1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
    2. The source of the noncompliance data
    3. The results of root cause analysis
    4. What action(s) were taken in response.

c. Healthcare provider non-compliance

i. Number and percentage of (b) (4) that were written by non-certified healthcare providers among all dispenses of Blenrep
    1. For all dispenses of Blenrep that were prescribed by a non-certified healthcare provider, a summary including whether an ophthalmic exam was obtained, (b) (4) whether the healthcare provider later became certified, and if so, the time elapsed between dispenses and healthcare provider certification.
ii. Number of healthcare providers who became decertified as a result of non-compliance, accompanied by a summary of reasons for decertification

d. Healthcare setting non-compliance

i. Number and percentage of (b) (4) by non-certified healthcare setting among all dispenses of Blenrep.
    1. For all dispenses of Blenrep by non-certified healthcare setting, a summary including whether an ophthalmic exam was obtained, (b) (4)

[redacted] whether the healthcare setting later became certified, and if so, the time elapsed between dispenses and healthcare setting certification

ii. Number and percentage of [redacted] to non-enrolled patients among all dispenses of first dose of Blenrep

1. For all dispenses of Blenrep to non-enrolled patients, a summary including whether an ophthalmic exam was obtained, [redacted] whether the patients later became enrolled, and if so, the time elapsed between dispenses and patient enrollment.

iii. Number and percentage of [redacted] to non-eligible patients among all dispenses of subsequent doses of Blenrep.

1. For all dispenses of Blenrep to non-eligible patients, a summary including whether an ophthalmic exam was obtained, [redacted], and if a Patient Status Form was received

iv. Number and percentage of [redacted] that were written by non-certified healthcare providers for non-enrolled patients at non-certified healthcare setting among all dispenses of Blenrep

1. For all dispenses of Blenrep that were written by non-certified healthcare provider for non-enrolled patients at non-certified healthcare setting, a summary [redacted] whether an ophthalmic exam was obtained, [redacted] whether the patients later became enrolled, whether healthcare provider and healthcare setting later became certified, and if so, the time elapsed between dispenses and patient enrollment and prescriber and healthcare setting certification

v. Number and percentage of [redacted] that bypassed the REMS verification process among all dispenses of Blenrep

1. For all dispenses of Blenrep that bypassed the REMS verification process, a summary [redacted] whether an ophthalmic exam was obtained, [redacted] healthcare provider certification status, patient enrollment status, and whether a current Patient Status Form is received.

vi. The number of healthcare setting that became decertified as a result of non-compliance, accompanied by a summary of reasons for decertification

e. Wholesaler/distributor non-compliance

i. Number and percentage of shipments distributed by non-authorized wholesaler or distributor

ii. Number and percentage of Blenrep shipments distributed to non-certified healthcare settings

Safe Use Behaviors

7. Patient Status Forms (provide for each reporting period and cumulatively)

    a. Number and percentage of patients with (b) (4) corneal adverse reaction (b) (4) stratified by dose cycle (e.g. 1st, 2nd, 3rd, or 4th dose). Provide a summary and data in a tabular format.
    b. Number and percentage of patients who did not have a Patient Status Form submitted prior to each infusion among (b) (4) stratified by dose cycle (e.g. 1st, 2nd, 3rd, 4th dose). Provide a summary and tabular format.
        i. For all patients who did not have a Patient Status Form submitted prior to each dose, a summary of the reasons ophthalmic exam was not performed (b) (4) (b) (4) and the source of reason information (e.g., healthcare provider or patient) and root cause analysis
    c. (b) (4)
    d. (b) (4)
    e. Time between enrollment and first dose. Include a summary for reasons for delay.
    f. Number of patients who experienced a treatment interruption, including the duration of treatment interruption and reason for treatment interruption
    g. Number and percentage of patients who (b) (4) ophthalmic exam after the 14-day window expired

8. REMS Verification and Checklist

    a. (b) (4)
    b. Number and percentage of patients who had a REMS checklist submitted beyond the targeted timeframe of 5 days among all patients who were dispensed Blenrep. (b) (4)
    c. Number and percentage of times when the verification results indicate "DO NOT INFUSE." Include a summary of the reasons why patient is unable to receive the dose (e.g. provider is not certified, patient is not enrolled, no Patient Status Form)

9. Prescriber Treatment Modification Assessment (provide for each reporting period and cumulatively)

    a. Number and percentage of healthcare provider who documented that treatment was modified on the Patient Status Form for patients with (b) (4) corneal adverse events. Include the number and percentage of patients who had a Patient Status Form

documenting the prescriber recommending dose modification. Provide a summary and data in a tabular format.

b. Number and percentage of healthcare provider who did not modify treatment accordingly per the Prescribing Information for patients with (b) (4) corneal adverse events. Provide a summary and data in a tabular format.
    i. For patients with Grade 2 (moderate superficial keratopathy or decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200), a summary including whether Blenrep was withheld, if ophthalmic exam findings improved to Grade 1 or better, and whether treatment was restarted and at what dose.
    ii. For patients with Grade 3 (severe superficial keratopathy or decline from baseline by more than 3 lines on Snell Visual Acuity and not worse than 20/200), a summary including whether Blenrep was withheld, if ophthalmic exam findings improved to Grade 1 or better, and whether treatment was restarted a reduced dose.
    iii. For patients with Grade 4 (corneal epithelial defect or Snellen Visual Acuity worse than 20/200), a summary including whether treatment was discontinued

Knowledge

10. Knowledge Assessments (provide for each reporting period and cumulatively)

    a. The number of completed post-training knowledge assessments for healthcare providers, including the method of completion and the number of attempts to complete.
    b. A summary of the most frequently missed knowledge assessment questions.
    c. A summary of potential comprehension or perception issues identified with the knowledge assessment.

11. Stakeholder Survey (beginning with the 2-year assessment report and every other year thereafter)

    a. Healthcare provider survey to assess if healthcare providers are educated on the following:
        i. The risk of ocular toxicity associated with the use of BLENREP
        ii. The need to submit documentation that ophthalmic exams are being done at baseline and prior to each dose to identity ocular toxicity
        iii. The need to counsel patients on the risk of ocular toxicity and the requirement for monitoring via ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms as described in the Prescribing Information.

Health Outcomes and/or Surrogates of Health Outcomes

(b) (4)

a. (b) (4)

13. Safety Surveillance (provide for each reporting period and cumulatively)

    a. Known, or suspected [redacted] (b) (4) corneal adverse reactions are to be reported regardless of outcome. Provide an overall analysis and discussion of all cases identified from all sources (i-iv):
        i. Patient Status Form
        ii. Spontaneous adverse event reports
        iii. Literature searches
        iv. Social media
        v. Call center

    b. The overall analysis and discussion on [redacted] (b) (4) corneal adverse reactions including but not limited to:
        i. For each patient with a [redacted] (b) (4) corneal adverse reaction, a summary including whether an ophthalmic exam was conducted prior to each dose, the number of ophthalmic exams missed/skipped, progression of keratopathy or changes in visual acuity at each ophthalmic exam, appropriateness of treatment modification, whether there were improvements to a Grade 1 or better, if treatment was restarted or discontinued, and if restarted, whether the dose was restarted at the same or reduced dose. Provide a summary and data in a tabular format.
        ii. Patient age (Median, Range)
        iii. Patient age group (<18, 18 to 64, 65 to 74, ≥75)
        iv. Total Dose (Mean, Range)
        v. Dose per cycle (mg/kg/dose)
        vi. Cumulative Time to Event Analysis, stratified by patient age group, Total Dose (Mean, Range), Dose per cycle (mg/kg/dose)

    c. For Grade 2, 3 and 4 corneal adverse reaction, stratified by age group and dosing to include:

        i. Number of cases requiring hospitalization
        ii. Number of cases leading to dose reduction
        iii. Number of cases leading to dose interruption/delay
        iv. Number of cases [redacted] (b) (4)

    d. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

14. The requirements for assessments of an approved REMS under section 505- 1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Carolyn Tieu, Pharm.D., MPH, Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 27, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Blenrep (belantamab mafodotin-blmf). On December 5, 2019, GlaxoSmithKline Intellectual Property Development Ltd. (GSK) submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) (b) (4) (b) (4) This application is under review in the Division of Hematology Malignancies 2 (DHM2).

The Applicant's proposed REMS submitted on July 7 (email), July 10 (Global Submit; GS), July 17 (email), July 21 (GS) and July 24 (email), 2020 are the subject of this review. Their proposed REMS consists of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Materials Reviewed

General comments on the Applicant's REMS document, REMS Supporting Document and REMS materials were provided on June 26, 2020. On July 10, 2020, the Applicant provided responses to the Agency's comments. FDA provided comments on July 22, 2020, on attestations for the prescriber, healthcare setting and patient enrollment forms, which have been reviewed by the Offices of Regulatory Policy (ORP) and Chief Counsel (OCC). We also provided comments on the Eye Care Professional Consult Request Form, Patient Status Form, REMS Checklist, Education Program for Prescribers and Prescriber Knowledge Assessment. In addition to the review by the DRM, the REMS Document has been reviewed by the OCC. The revisions to this document include OCC's comments.

The following materials have been reviewed and comments on these materials are appended to this review:

- REMS Document
- REMS Supporting Document

3 Comments to the Applicant

The Agency has reviewed the proposed REMS Document and REMS Supporting Document, submitted on July 7 (email), July 10 (Global Submit; GS), July 17 (email), July 21 (GS) and July 24 (email), 2020. Please see the summary of comments below, as well as the redlined changes and specific comments provided in each document attached.

In order to facilitate further review, we ask that you respond to these comments by **July 29, 2020**. The next submission to the Gateway should include Clean MS Word, Tracked MS Word (if applicable), and final formatted pdf or PowerPoint versions of these materials.

General Comment

If approved, when do you anticipate marketing of your product?

I. REMS Document

Your proposed REMS document follows the draft guidance for Industry Format and Content of the REMS; however, additional edits are necessary to align with the REMS document template to support standardization of the format and content of REMS. In addition, the REMS and all the REMS materials will need to align with final labeling.

A summary of the significant additions and deletions are listed below.

1) Since the is about informing the patient of the requirement to enroll if they want to get Blenrep, the the 4th goal has been revised to include, "the requirement" for further clarification.

2) Maintain "healthcare providers" (b) (4) to be consistent with #1 "healthcare providers who prescribe" and to conform to the statute and REMS document template.

3) Edits are needed to align with the REMS document template to support standardization of the format and content of a REMS document for #7 and #9 under "III.REMS Requirement 1. Healthcare Providers who prescribe Blenrep must:" The proposed "Template adaptation" language can be included under "to support REMS Program operations" as #7.

4) Please remove (b) (4) from the REMS document. The Agency believes that this would be more appropriately captured (b) (4) (b) (4)

5) The titles of each section of the REMS template must be maintain as they align with the statute and support standardization of the format and content of a REMS document. Therefore, please keep "dispense" in the title and the word "administer" in the text for further clarification regarding the infusion of the drug.

6) In the section, To support REMS Program operations, GlaxoSmithKline must, we have modified #1 and #7 for further clarification and added the following language (#9) to support REMS Program operations.

> 1. Authorize dispensing for each patient based on receipt of the Patient Enrollment Form and Patient Status Form on the following schedule: Authorize the first dispensing upon receipt of the Patient Enrollment Form and Patient Status Form. If a completed Patient Enrollment Form and Patient Status Form are not received, the patient is not authorized to receive the drug. For subsequent dispensing, authorize dispensing based on receipt of the Patient Status Form. The authorization is valid for 14 calendar days from receipt of the Patient Status Form.

7. Ensure prescribers are able to use the Eye Care Professional Consult Request Form by fax and to adapt it as a template to use within healthcare information technology system software.

9. Ensure healthcare settings are able to complete and submit the REMS Checklist by [insert mechanisms].

7) Audits - Your proposal (b) (4) (b) (4) is not appropriate. (b) (4) (b) (4) (b) (4) Failing to address potential non-compliance events in a timely manner may ultimately put patients at risk for ocular toxicity. Audit all certified health care settings no later than 90 calendar days after they have dispensed Blenrep, and once every 3 years thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.

8) The Agency believes that you should audit wholesalers-distributors no later than 90 calendar days after they become authorized to distribute Blenrep and annually thereafter.

9) Under the heading, To ensure REMS participant compliance with the REMS program GlaxoSmithKline must… , item # 24, delete the statement (b) (4) (b) (4) in the REMS document. This is covered by #19 – establish a plan for addressing noncompliance. This can be explained in REMS Supporting Document.

II. REMS Supporting Document

Align the REMS Supporting Document with the REMS Document and label.

III. REMS Assessment Plan

The assessment plan is undergoing discussion in the Agency and additional comments or edits will be forthcoming.

IV. REMS Audit Plan

Because of the healthcare setting's critical role in the REMS, it is very important to the Agency that you provide a sound and rigorous methodology. In general, using a multimodal approach would reduce bias and strengthen the validity of your findings. A multimodal approach may consist of remote audits, such as an email/mail questionnaire or scripted telephone questionnaire, and on-site audits. You should submit an audit plan that describes, at a minimum, the scope of your audits, including when you will use a risk-based approach for auditing, and methods used.

Provide a description of how many healthcare settings, healthcare providers and patients do you anticipate to be certified or enrolled in the REMS in the first, second and third years after marketing. These estimated should be used in considering the number of sites you will need to include in your sample.

If approved, submit your protocol within 90 days from the date of approval, including an appropriate timeframe for implementation. Confirm your acknowledgement.

V. REMS Non-Compliance Plan

To ensure the REMS is functioning as intended, you must develop a plan to define non-compliance events, the severity of the non-compliance events (minor, major, critical), and the corrective actions that may be taken to address it (e.g. 1st event – re-education/retraining; 2nd event – re-education/retraining; 3rd event – re-education and a warning with a corrective and preventative plan; 4th event – deactivation). See table in appendix A.

A pre-determined threshold needs to be developed for patients who may not comply with consecutive ocular exams. This threshold is critical to assist with assessing whether the REMS is meeting its goal and objectives and whether further regulatory action is warranted. The Agency recognizes that 100% compliance is rarely achieved in a real-world setting. You should carefully consider pertinent compliance data from clinical trials and how this may translate into a real-world setting. Provide a threshold and your rationale for this threshold.

If approved, submit your protocol within 90 days from the date of approval, including an appropriate timeframe for implementation. Confirm your acknowledgement.

Appendix A. Example of Non-Compliance Plan

Stakeholder	**Non-Compliance Events**	**Source of Non-Compliance Events**	**Severity Level**	**Corrective actions that may be taken (e.g. reeducation, deactivation)**
Healthcare settings	Dispensed Blenrep to a non-enrolled patient	Audit or spontaneous event reported	Critical	
Healthcare settings	Dispensed Blenrep to a non-eligible patient	Audit or spontaneous event reported	Critical	
Healthcare settings	Dispensed Blenrep to a non-enrolled patient, with a non-certified prescriber, at a non-certified healthcare setting.	Audit or spontaneous event reported	Critical	
Healthcare settings	Dispensed Blenrep after obtaining a "Do Not Infuse" status	Audit or spontaneous event reported	Critical	
Healthcare settings	Dispensed Blenrep by bypassing the generation of an authorization code to an enrolled or eligible patient	Audit or spontaneous event reported	Major	

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 22, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Blenrep (belantamab mafodotin-blmf). On December 5, 2019, GlaxoSmithKline Intellectual Property Development Ltd. (GSK) submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) This application is under review in the Division of Hematology Malignancies 2 (DHM2).

The Applicant's proposed REMS submitted on May 7, 2020 are the subject of this review. Their proposed REMS consists of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Materials Reviewed

General comments on the Applicant's REMS document, REMS Supporting Document and REMS materials were provided on June 26, 2020. On July 10, 2020 the Applicant provided responses to the Agency's comments. In addition to the review by the DRM, the attestations for the prescriber, healthcare setting and patient enrollment forms have been reviewed by the Office of Chief Counsel (OCC). The revisions to these materials include OCC's comments.

The following materials have been reviewed and comments on these materials are appended to this review:

- Attestations for the prescriber, healthcare setting and patient enrollment forms
- Eye Care Professional Consult Request Form
- Patient Status Form
- (b) (4) Checklist
- Prescriber Education
- Prescriber Knowledge Assessment

3 Comments to the Applicant

The Agency has reviewed the proposed **Eye Care Professional Consult Request Form, Patient Status Form,** (b) (4) **Checklist, Prescriber Education and Prescriber Knowledge Assessment** submitted on May 7, 2020. Note that the attestations have been revised are provided at the beginning of the PDF file of the compiled materials. Replace the attestations in your Prescriber, Healthcare Setting, and Patient Enrollment forms with these. Please see the summary of comments below, as well as the redlined changes and specific comments provided in each document attached.

In order to facilitate further review, we ask that you respond to these comments by **July 24, 2020**. The next submission to the Gateway should include Clean MS Word, Tracked MS Word (if applicable), and final formatted pdf or PowerPoint versions of these materials.

Eye Care Professional Consult Request Form

We have revised the introduction and instructions. A brief statement of the risk is included, along with the purpose of the form and simple instructions.

Additional clarifications and edits for the corneal examination and best corrected visual acuity findings are included. Include the following in the Eye Care Evaluation Guide:

- "Normal" as a grading scale category
- A column with check boxes for reporting the grade for the worst eye

Patient Status Form

The Ophthalmologic Assessment questions should align with that Eye Care Professional Consult Request Form Template for ease of oncologist use. Include a question on current grading from the examination find and BCVA. Include "Normal" as a grading scale category in the Dosage Modification's for Corneal Adverse Reactions pre the Keratopathy and Visual Acuity (KVA) Scale chart in the form.

(b) (4) **Checklist**

We have made formatting and other content edits to the form. Changing the name of the checklist to "REMS Checklist" is acceptable.

Education Program for Prescribers

The Education Program for Prescribers should focus on the risk of ocular toxicity and associated adverse events. Delete content that is not included in the Prescribing Information. Presentation of risk information from clinical trial data should come from the Warnings and Precautions section of the Prescribing Information. Include a slide describing dose recommendations before the dosing modifications are discussed. REMS Program content must be revised to clarify program requirements.

Prescriber Knowledge Assessment

Remove content that has also been removed from the prescriber education. The number of questions on the REMS program can be reduced. Include another question specific to the risk of ocular adverse reactions include keratopathy and changes in visual acuity, blurred vision, and dry eyes. Include a question concerning dosing modification based on eye exam results.

BLENREP REMS Attestations

Healthcare Providers

I have:

- Reviewed the drug's **Prescribing Information**.
- Reviewed the Program Overview and Education Program for Prescribers.
- Successfully completed the Knowledge Assessment and submitted it to the BLENREP REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient, using the Patient Guide, on the
    - the risk of ocular toxicity associated with Blenrep and
    - requirement for monitoring via ophthalmic examinations (e.g., visual acuity and slit lamp) at
        - baseline,
        - prior to each dose, and
        - promptly for worsening symptoms

- Enroll the patient by completing and submitting the Patient Enrollment Form to the BLENREP REMS.

- Assess the patient's ocular health by consulting an eye care professional to complete the visual acuity and slit lamp examinations using the Eye Care Professional Consult Request Form.

- Assess the patient's ophthalmic consult results for appropriateness of initiating treatment. Document and submit to the BLENREP REMS using the Patient Status Form.

Before each infusion, I must

- Assess the patient's ocular health by consulting an eye care professional to complete visual acuity and slit lamp using the Eye Care Professional Consult Request Form.

- Assess the patient's ophthalmic consult results for appropriateness of continuing treatment. Document and submit to the REMS Program using the Patient Status Form.

Patients

Before I start treatment, I must

- Receive counseling from my prescriber using the Patient Guide.
- Enroll in the BLENREP REMS by completing the Patient Enrollment Form with my prescriber.
- Get an eye exam.

During my treatment and before each infusion, I must

- Get an eye exam.

At all times

- I must inform my prescriber if I have any signs or symptoms of worsening eyesight or eye health including**:**
    - Blurry vision
    - Dry eyes
    - Worsening vision
- I understand GlaxoSmithKline and its agents may use and share my personal information to enroll me into and manage the BLENREP REMS. Information about all patients who get BLENREP will be stored in a private and secure database. My health information may be shared with the U.S. Food and Drug Administration (FDA) to evaluate the BLENREP REMS. However, my name will not be shared.
- I give permission for the GlaxoSmithKline and its agents to contact me or my prescriber by phone, mail, or email to manage the BLENREP REMS.

Healthcare Settings

As the Authorized Representative:

- I have reviewed the drug's **Prescribing Information**.
- I have reviewed the Program Overview and Education Program for Health Care Settings**.**
- I must train all relevant staff involved relevant staff involved in dispensing and administering BLENREP using the Program Overview and Education Program for Health Care Settings**.**
- I must establish processes and procedures to the REMS Checklist is completed and submitted for each patient.

On behalf of the healthcare setting, I must comply with the following REMS requirements:

Before administering each dose:

- Obtain authorization to dispense each dose by contacting the BLENREP REMS to verify
  - The prescriber is certified in the BLENREP REMS
  - The patient is enrolled in the BLENREP REMS and authorized to receive this dose of BLENREP
- Complete the REMS Checklist

After administering BLENREP, within 5 business days:

- Submit the REMS Checklist it to the BLENREP REMS.

At all times:

- Not re-distribute, transfer, loan or sell BLENREP.
- Maintain records documenting staff completion of REMS training.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by GlaxoSmithKline or third party acting on GlaxoSmithKline's behalf to ensure that all processes and procedures are in place and are being followed.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Carolyn Tieu, Pharm.D., MPH, Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 26, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

Table of Contents

1 Introduction

This review evaluates and provides comments on the risk evaluation and mitigation strategy (REMS) proposal for Blenrep (belantamab mafodotin-blmf), submitted by GlaxoSmithKline Intellectual Property Development Ltd. (GSK) on December 5, 2019.

GlaxoSmithKline Intellectual Property Development Ltd. (Applicant) submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4)

The Applicant was informed that a REMS that included elements to assure safe use (ETASU) would be needed to ensure the benefits outweigh the risk of ocular toxicity.

The Applicant's proposed REMS submitted on April 13, 2020 and May 7, 2020 are the subject of this review. Their proposed REMS consists of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Background

2.1 Product Information

Blenrep (belantamab mafodotin-blmf), new molecular entity, is a B-cell maturation antigen (BCMA)-directed antibody-drug conjugate. Upon binding to BCMA, Blenrep is internalized followed by release of free cytotoxic drug monomethyl auristatin F (cys-mcMMAF) via proteolytic cleavage. The released MMAF intracellularly disrupts the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin-blmf is prepared as 100 mg lyophilized powder in a single-dose vial for reconstitution. The recommended dose of belantamab mafodotin-blmf is 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion. Ocular adverse reactions occurred in 77% of 218 patients in the pooled safety population in clinical trial. The most common finding was reported on eye examination as keratopathy (76%) or changes in visual acuity (55%). Other common adverse reactions included blurred vision (27%) and dry eye (19%). Examination findings were not always accompanied by either symptoms or changes in visual acuity. Among patients with keratopathy (n = 165), 49% of patients had ocular symptoms, 65% had a change in visual acuity (2 lines or more Snellen score in any eye), and 34% had both ocular symptoms and visual acuity changes. Belantamab mafodotin-blmf breakthrough therapy designation on October 27, 2017. Belantamab mafodotin-blmf is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for belantamab mafodotin-blmf (BLA 761158) relevant to this review:

- 01/31/2014: Investigation New Drug (IND) 119333 submission for belantamab mafodotin-blmf (GSK2857916) was received.
- 10/27/2017: Breakthrough Therapy designation granted
- 12/05/2019: BLA 761158 submission for belantamab mafodotin-blmf with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4) received.
- 01/28/2020: Applicant was informed that the ocular toxicity warrants a boxed warning, and a REMS, and encouraged the Applicant to think about a detailed REMS plan to ensure adequate and frequent assessment of vision.
- 02/11/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, FDA has determined that a REMS will be necessary to ensure that the benefits of belantamab mafoditin-blmf outweighs the risk of ocular toxicity. The review team will provide feedback on Applicant's proposal and the necessary REMS elements, after agency has reviewed the proposal, which is expected on or before February 17, 2020.
- 02/18/2020: The Applicant submitted communication plan REMS to mitigate the risk of ocular toxicity.
- 04/13/2020: The amended submission for BLA 761158 received from the Applicant. The amended submission included the proposed REMS consists of communication plan, ETASU, an implementation system, and a timetable for submission of assessments to mitigate the risk of ocular toxicity.
- 05/07/2020: The amended submission for BLA 761158 received from the Applicant. The amended submission included the REMS document, REMS Supporting Document and REMS Appended Materials.
- 05/12/2020: REMS Oversight Committee (ROC) meeting[1] was held to discuss the REMS with ETASU to mitigate the risk of ocular toxicity for belantamab mafoditin-blmf. The ROC unanimously concurred with DRM/DHM2 recommendation that the REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of belantamab mafodotin-blmf to outweigh the risk of ocular toxicity.

3 Review of Applicant's REMS Submission and DRM Comments

3.1 REMS Goals

The Applicant submitted a proposed goal(s). The goal of the BLENREP REMS is to manage the risk of (b) (4) by:

1. (b) (4)

[1] As per the 21st Century Review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Office of New Drugs, Surveillance and Epidemiology, and the Office of Regulatory Policy.

(b) (4)

2. Ensuring safe use of BLENREP by:
    a. (b) (4)
    b. Ensuring that BLENREP is infused in certified healthcare settings only after verification of ophthalmic examination
3. Ensuring that patients are informed about:
    a. the risk of (b) (4) associated with the use of BLENREP
    b. the requirement for (b) (4) ophthalmic examinations at baseline, prior to each dose and promptly for worsening symptoms, as described in the Prescribing Information
4. (b) (4)

Reviewer Comment: *Overall, we agree, with the applicant's proposed goals with some additional modifications. We have determined that the healthcare providers need to be educated and will be required to submit documentation of the ocular monitoring. The 1st objective has been revised to include, "adhere" and the requirement of submission of documentation had been added to the goal. The Applicant must also align the REMS document with the label which includes "ocular toxicity" instead of* (b) (4)

In 2nd objective, overall we agree with Applicant's proposal to document that that ocular exams were performed at baseline prior to the treatment. The Agency is still considering balancing safe use conditions and the burden to stakeholders with regard to the intervals at which ocular exams needed to be documented.

(b) (4) *Therefore, the Applicant's last goal:* (b) (4) *can be removed.*

DRM is proposing the following changes to the goal and objectives for the Blenrep REMS.

The goal of the BLENREP REMS is to manage the risk of ocular toxicity by:

1. *Ensuring that healthcare providers are educated on the risk of ocular toxicity associated with the use of BLENREP*
2. *Ensuring that healthcare providers are educated and adhere to the following:*
    a. *submit documentation that ophthalmic exams are being done at baseline and prior to each dose to identify ocular toxicity*
    b. *counsel patients on the risk of ocular toxicity and the requirement for monitoring via ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms as described in the Prescribing Information*
3. *Ensuring safe use of BLENREP by:*
    a. *Ensuring that BLENREP is infused in certified healthcare settings only after verification of ophthalmic exams*
4. *Ensuring that patients are informed about:*
    a. *the risk of ocular toxicity associated with the use of BLENREP*

b. *the requirement for ophthalmic exams at baseline, prior to each dose and promptly for worsening symptoms, as described in the Prescribing Information* (b) (4)

3.2 REMS Document

The REMS document includes ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring). Additionally, it includes an implementation system to ensure that the applicant is implementing and maintaining the REMS requirements and a timetable for submission of assessments.

Reviewer Comments: *The REMS document was submitted and aligns with the draft guidance for Industry Format and Content of the REMS[2]; however, there are additional edits needed to align with the REMS template to support standardization of the format and content of a REMS document. DRM has provided edits in track changes in REMS Document and is attached.*

3.3 REMS Elements

3.3.1 Elements to Assure Safe Use

The next several sections cover the specific details proposed in the ETASU A, B, D and E.

3.3.1.1 Blenrep will be prescribed only by a certified healthcare provider

The Applicant is proposing that prescribers are required to be educated and certified in the Blenrep REMS in order to prescribe. In order to become certified, the prescriber must: review the Blenrep Prescribing Information, review the REMS Program Overview and Prescriber Training, successfully complete and submit the Knowledge Assessment to the Blenrep REMS and enroll in the REMS Program by completing and submitting the Prescriber Enrollment Form to the REMS.

Prescribers must also attest when they enroll in the REMS that they understand they need to ensure that patients have baseline ophthalmic examinations performed prior to treatment and before each dose. As described in section 2 of labeling, based on the results of the ophthalmic examinations, dose modifications maybe necessary to mitigate the risks of ocular toxicity. Additionally, prescribers need to counsel patients about the ocular toxicity and enrollment each patient in the REMS prior to starting a patient on Blenrep.

Reviewer Comment: *The Applicant must align the REMS document with the label which includes "ocular toxicity" instead of* (b) (4)

Before treatment initiation, the REMS should include that the prescriber needs to assess the patient's ocular health by consulting an eye care professional to perform and complete visual acuity and slit lamp using the Eye Care Professional Consult Request Form. The consult form is to assist the oncologist in

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-and-content-rems-document-guidance-industry (accessed 6/5/20)

managing corneal toxicities by facilitating the findings of the eye exam and connect these findings to the recommendations for dosage modifications as outlined in section 2 (Dosage Modifications for Adverse Reactions) of labeling. The ophthalmologist should report the findings to the prescriber using the Eye Care Professional Consult Request. The form should align with section 2 of labeling, including Table 1. Dosage Modifications for Corneal Adverse Reactions per the Keratopathy and Visual Acuity (KVA) Scale. We have determined that changes are needed in section III.1.Before treatment initiation (first dose).7 & 8. as outlined below (the new text is underlined):

> *7. Assess the patient's ocular health by consulting an eye care professional to complete visual acuity and slit lamp examinations using the Eye Care Professional Consult Request Form.*
>
> *8. Assess the patient's ophthalmologic consult results for appropriateness of initiating treatment. Document and submit to the REMS Program using the Patient Status Form.*

The same texts are inserted in section III, 1. During treatment; before each infusion.9 & 10.

Other edits were made in section III. 1. At all times, 12 for clarity and to ensure consistency with other REMS programs.

3.3.1.2 Blenrep will be dispensed only to the enrolled patients

The Applicant is proposing that Blenrep be dispensed only to patients, who are enrolled in the REMS program. This ensures that patients are educated on the risk of ocular toxicity of Belnrep and the need for monitoring.

Reviewer Comment: *We agree that patient enrollment is necessary to ensure that patients are informed of the risks and the need for monitoring. We do not agree with the Applicant's proposal* (b) (4) (b) (4) *The patient will be enrolled in the program, counseling by the prescriber and the patient will be provided in a Blenrep Patient Guide. The information* (b) (4) *is redundant* (b) (4) *therefore, this material can be removed from the REMS.*

This reviewer does not object to the Applicant developing (b) (4) *materials* (b) (4) *that are outside of the REMS. It is not uncommon for companies to provide additional patient support services; however, these materials should not be included in the REMS. The Office of Prescription Drug Labeling Promotion (OPDP) has advised that the Applicant's proposed non-REMS materials should be submitted to OPDP for review as they are not part of labeling or the REMS.*

3.3.1.3 Blenrep will be dispensed only to patients in a certified healthcare setting

The Applicant is proposing that Blenrep is dispensed only in healthcare settings that are certified. Certified healthcare settings will be required to verify that healthcare prescribers are certified, patients are enrolled and authorized to receive the dose of Blenrep prior to administering Blenrep to patients.

Reviewer Comment: *The title of this section has been revised to: " Healthcare Settings that dispense BLENREP must". Healthcare settings need to verify that the prescriber is certified in the REMS, the*

patient is enrolled and authorized to receive that dose of Blenrep. As outlined in the REMS document, the authorization is completed by contacting the REMS Program. The Applicant needs to provide the rationale and the functionality of completing the (b) (4) *Checklist for each patient prior to the infusion. Please add details of how this activity supports program implementation and/or the safe use conditions to the REMS Supporting Document.*

The Agency's current thinking is to minimize burden to stakeholder and not require the healthcare setting authorized representative to re-enroll annually.

We have determined to revise the language as outlined below in section III.3.To maintain certification to dispense.9. (the new text is underlined):

> *9. Have the authorized representative <u>enroll</u> in the REMS Program by completing and submitting the Healthcare Setting Enrollment Form to the REMS program.*

3.3.1.4 Blenrep will be distributed only to certified healthcare setting

The proposed REMS did not include a section on wholesalers-distributors that distribute Blenrep and what wholesalers-distributors need to do to ensure that Blenrep is only distributed to certified health care settings.

Reviewer Comment: *Distribution by wholesalers was discussed with the Applicant during the April 28, 2020 teleconference and provided as written comments on May 5, 2020, based on the REMS proposal submitted on April 13, 2020. The Agency communicated to the Applicant that if wholesalers-distributors are involved in the process, this REMS requires a Wholesaler Enrollment Form would need to be included in the Supporting Document. The applicant did not submit this form.*

In the response to the Agency's Information request on May 5, 2020, received on May 7, 2020, the Applicant stated that wholesalers-distributors are not directly involved in the REMS process as control points; rather distribution is being controlled at the patient level at the site of administration through the healthcare setting (HCS) participation in the program. Therefore, Applicant believes that a Wholesaler Enrollment Form is not necessary for the BLENREP REMS program.

We do not agree with the Applicant's decision to exclude the wholesalers-distributors from REMS document. Since wholesalers-distributors can only distribute Blenrep to certified healthcare settings and the Applicant needs to ensure that this occurs. We have included language regarding the wholesalers-distributors in section III.4. for clarity, and to ensure consistency with other REMS programs. The Applicant need to describe in their Supporting Document their process for ensuring that wholesalers (e.g. enrollment, contracts) meet this requirement.

3.4 Communication Materials and Dissemination Plans

The Applicant proposed to send a Dear Healthcare Provider REMS Letter, a Professional Society Letter, a Fact Sheet (b) (4) to communicate that Blenrep is approved with REMS to mitigate the risk of ocular toxicity. The Applicant proposes to send the Factsheet with the REMS Letters and provide them during the initial discussion with healthcare providers for 12 months after Blenrep approval. The Factsheet messaging focuses on the risk of ocular toxicity and the REMS program. The Healthcare Provider letter and REMS Factsheet would target healthcare providers such

as oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, pharmacists and eye care professionals. The Applicant proposes (b) (4) The Applicant will send the REMS letter by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable. In addition, they are proposing to disseminate a similar letter to ophthalmology professional societies and associations. The Applicant proposed to email the REMS Letters within 30 calendar days of the date Blenrep is first commercially distributed, and again 12 months later.

The Applicant is also proposing (b) (4)

Reviewer Comment: *Since eye care professional are not included as stakeholders in the REMS, we have determined that the Healthcare Provider REMS Letter should only be sent to the healthcare providers, likely to prescribe, dispense or administer Blenrep, such as oncology nurses and pharmacists and modified the language under "Target Audience" as outlined below (the new text is underlined):*

> *Healthcare providers, likely to prescribe Blenrep, oncology nurses and pharmacists.*

(b) (4)

We are including additional language in the REMS regarding sending the second email if the first email is marked as unopened and sending another mail if the second email is marked as unopened. The Applicant should determine the calendar days in which they will send these follow-up communications. The new text is underlined.

> *b. Send a second email within xx calendar days of the date the first email was send if the first email is marked as unopened.*
>
> *c. Send by mail within xx calendar days of the date the second email was send if the second email is marked as unopened.*

We also do not agree with the Applicant's proposal (b) (4) *This material may be removed as part of the REMS.*

(b) (4) *In addition, the formatting of this Factsheet distracts from the user receiving the message. Recommendations to simplify the Factsheet so the risk messaging is not lost are provided. The Applicant will need to incorporate our recommendations and resubmit the Factsheet.*

3.5 Implementation System

The Applicant outlines the following components of the proposed implementation system.

Establish and maintain

- REMS website
- REMS program call center
- Establish and maintain a validated secure data base of certified prescribers and enrolled patients
- Ensure that healthcare setting are able to enroll by fax, mail and online
- Notify prescribers and healthcare setting
- Risk-based audit approach

Reviewer Comment: *We have additional changes are necessary to the implementation system for it to be acceptable. We have inserted the language regarding the accessibility of the database. The Applicant must provide prescribers access to the database of certified healthcare settings and their enrolled patients. The Applicant must also provide authorized wholesalers-distributors access to the database of certified healthcare setting.*

We have added the following languages in to support REMS Program operations:

> *1. Authorize dispensing for each patient based on receipt of the Patient Enrollment Form and Patient Status Form on the following schedule: Authorize the first patient shipment upon receipt of the Patient Enrollment Form and Patient Status Form. If a completed Patient Enrollment Form and Patient Status Form are not received, the patient is not authorized to receive drug. For subsequent dispensing, if the Patient Status Form is not received [insert timeframe], the patient is not authorized to receive drug.*
>
> *7. Ensure prescribers are able to use the Eye Care Professional Consult Request Form by fax and with healthcare software.*

We have added language to the document to ensure REMS participants compliance with the REMS program.

> (b) (4) *if the Patient Status Form is not received [insert timeframe], the patient is not authorized to receive subsequent drug shipments*

The Applicant states some aspects of the REMS program website may not be fully operational at launch. The REMS program must be fully operations for the drug to enter interstate commerce.

We do not agree with the Applicant's proposal (b) (4) *We have added that healthcare settings be audited no later than 90 calendar days after they become certified and*

annually thereafter. The applicant must also change the requirements to audit all wholesalers-distributors for no later than 90 calendar days after they become authorized to distribute the drug and annually thereafter to align with current REMS practices and to ensure REMS process and procedures are in place, functioning, and support the REMS program requirements.

The (b) (4) *are not part of REMS, should not be included in the REMS Document.*

The Applicant must include the Eye Care Professional Consult Request Form to the "Patient Care Forms" section under V. REMS Materials.

3.6 REMS Materials

The Applicant has proposed the following materials as a part of their proposed REMS:

- Healthcare Provider REMS Letter
- REMS Letter for Professional Societies
- Factsheet
- (b) (4)
- Program Overview
- (b) (4)
- Patient Enrollment Form
- Eye Care Professional Consult Request Form
- (b) (4)
- Prescriber Knowledge Assessment
- Prescriber Enrollment Form
- Patient Status Form
- Healthcare Setting Training
- Healthcare Setting Enrollment Form
- (b) (4) Checklist
- Website desktop and mobile screenshots

The Applicant also submitted the following materials that are not part of the proposed REMS. We will not be providing comments on these materials and these materials should be removed from the REMS.

(b) (4)

Healthcare Providers REMS Letter

The Healthcare Providers REMS Letter will be sent to healthcare providers likely to prescriber Blenrep, as well as oncology nurses and pharmacists. The letter will be emailed, with a follow up mailed letter if an email is unavailable or undeliverable. The letter will also be disseminated through field bases sales

and medical representatives and Professional Meetings. The applicant submitted only a mailed version of the letter.

***Reviewer Comment**: The applicant should submit the formatted email version of the letter. Edits were made to make the letter more concise.*

REMS Letter for Professional Societies

The REMS Letter for Professional Societies will be disseminated to relevant professional societies.

***Reviewer Comment**: Minor edits were made to make the letter more concise.*

Program Overview

The Program Overview is part of the training for both healthcare providers and the authorized representatives from healthcare settings. The content focuses mostly on the REMS program requirements with some risk information included.

***Reviewer Comment**: Edits were made to the risk information, to remove redundant information and to align with labeling. Formatting changes should be made so that the reader can easily move through the content. The applicant will need to make changes to the Program Overview.*

Patient Enrollment Form

Patients must be enrolled in the Blenrep REMS. As described in the REMS, the prescriber should review and sign the enrollment form with the patient. The enrollment form explains the risk messages and requirements in the attestations on the form.

***Reviewer Comment:** The attestations have been modified based on the current REMS Document; however, the documents are still under review and additional changes may be necessary. The applicant will need to revise the form.*

Patient Guide

Prescribers must counsel the patient using the Patient Guide. The Patient Guide explains the risks of ocular toxicity and the requirement to get eye examinations before starting treatment, prior to each dose and promptly for worsening treatment.

***Reviewer Comment:** Edits were made to provide concise information related to the risk of ocular toxicity and the requirements of the BLENREP REMS.*

Prescriber Enrollment Form

Prescribers must enroll in the BLENREP REMS. Attestations on the Enrollment Form state that prescribers must counsel patients on the risk of ocular toxicity and assess a patient's vision before each infusion. Prescribers must submit the Prescriber Enrollment Form to the REMS.

Reviewer Comment: *The attestations have been modified based on the current REMS Document and are going through internal review. The applicant will need to revise the form.*

(b) (4)

The (b) (4) is part of the required training for representatives from healthcare settings. The content focuses mostly on the REMS program requirements with some risk information included. The applicant did not present the requirements for the healthcare settings clearly, and did not include information about using the website portal as part of the verification process.

Reviewer Comment*: The education does not clearly show the steps to obtain authorization to administer each dose of BLENREP. The presentation of the purpose of the* (b) (4) *Checklist and Patient Status Form is confusing. Required actions regarding the forms are not presented clearly. The website portal is not mentioned in the training. The applicant will need to revise the education to address our comments.*

Healthcare Setting Enrollment Form

Authorized representatives must enroll in the Blenrep REMS by completing the Healthcare Setting Enrollment Form and submitting to the REMS. Attestations on the Enrollment Form align with the requirements in the REMS Document, including contacting the REMS to verify the prescriber is certified, the patient is enrolled authorized to receive the drug. The healthcare setting representative must also complete the (b) (4) Checklist and submit to the REMS within 5 days. The applicant included a section (b) (4)

Reviewer Comment: *The Applicant should consider removing the section* (b) (4) *The attestations have been modified based on the current REMS Document and are going through internal review. The applicant will need to revise the form.*

Website desktop/ mobile

The Blenrep REMS will have a website to support implementation of the REMS. The applicant did not submit screenshots showing functionality of the REMS. In addition, the applicant proposes a portal to be used by healthcare providers for verification of REMS requirements. The applicant did not submit any screenshots of the portal. The applicant states that there will be an Eye Care Locator listed on the website. There is also a proposed (b) (4) is not a part of the REMS.

Reviewer's Comment*: The Applicant should include the functionality of the REMS website and portal. All comments on the REMS materials should be applied and included in the presentations of the website screenshots. We do not agree with the Applicant's proposal* (b) (4) *These resources would be more appropriate on a patient support page.*

3.7 REMS Assessment Timetable

The Applicant proposed to submit the REMS assessments (b) (4)

Reviewer Comments: *The applicant proposed REMS assessment timetable is not acceptable. The Applicant must submit the REMS assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.*

4 REMS Supporting Document

The REMS Supporting Document contains the REMS program background information, the goal, the REMS requirements, information for conducting REMS assessments, the REMS assessment timetable, and a description of the operations of the REMS.

Reviewer Comments:

1. *General, comments: The applicant must align the REMS Document with the REMS Supporting Document and labeling.*
2. *Include a brief description of REMS in section 2.2 REMS Goals and Objectives as outlined below:*
    a. *Prescribers who are certified in REMS and agree to comply with the REMS requirements can prescribe*
    b. *Prescribers must counsel*
    c. *Prescribers must enroll each patient*
    d. *Evaluation of Patient status form*
    e. *Only healthcare settings who are certified can administer*
    f. *Only wholesalers-distributors who agree to comply with the REMS requirements can distribute*
3. *The Applicant must provide a step by step detailed description of Healthcare Provider certification process in section 2.5.2. Healthcare Provided REMS Requirements. The Applicant must provide a detailed description of how the Knowledge Assessment is conducted, evaluated and graded and how prescribers will be notified to address incorrectly answered questions, in this section as outlined below:*

    Other descriptions like:

    1. *How many attempts are allowed to certify?*
    2. *Ineligibility criteria – e.g. as follows:*
        a. *If not successfully completed after "x" attempts, the prescriber will be ineligible to certify.*
        b. *Ineligible prescribers who request to have their ineligible status removed will be contacted by a "sponsor" representative who will determine whether to remove the ineligible status on a case-by-case basis.*
        c. *If the ineligible status is removed, the prescriber will be instructed to rereview the Prescribing Information, Program Overview, Prescriber Training, and will have an additional "x" attempts to become certified.*
4. *It is not clear how the drug is distributed to the Healthcare Setting. The Applicant must provide information whether the drug only shipped to the Healthcare Setting for a specific patient.*

5 REMS Assessment Plan

Audit/Compliance Protocols Comments:

- *Submit an audit protocol as an appendix to the REMS Supporting Document that includes, but not limited to: objective and scope of the audits, methods used for audits, and types of corrective actions that may be taken to address noncompliance*
- *You noted that a plan will be established for addressing noncompliance with the REMS program requirements. Explain this plan, including, but not limited to: establishment of a Compliance Review Committee, the scope and clear definitions of non-compliance examples, and actions that may be taken to correct and prevent future occurrences (e.g. warnings, suspension, deactivation, recertification). Submit a non-compliance protocol as an appendix to the REMS Supporting Document.*

AP Comments:

- *Refer to the draft guidance "Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry" released in January 2019 for further guidance on conducting REMS assessment surveys including study design, survey instrument development, sampling, survey data collection and processing, and data analysis. You propose a knowledge survey to evaluate healthcare provider's understanding of the corneal adverse reactions associated with Blenrep and the need to counsel patients regarding the risk and the need for baseline and regular ophthalmic exams. Discuss the feasibility of conducting a survey in this population and provide the rationale for using 80% as the target level for comprehension. Include the estimated size of the healthcare provider population for each year in the next 7 years. If a survey is not feasible, include other approaches to evaluate knowledge.*
- *For the Communication Plan, include metrics to measure the extent to which the REMS materials reached the intended stakeholders.*
- *Refer to the draft guidance "REMS Assessment: Planning and Reporting" released in January 2019 for further guidance on developing and formatting an assessment plan. Provide a table that outlines how each of the objectives of the goal will be met. See example in Appendix A in the last page.*

6 Comments to the Applicant

The Agency has reviewed your proposed Blenrep REMS Document, REMS Supporting Document, and REMS materials submitted on February 18, 2020, April 13, 2020 and May 7, 2020. The comments in the attached red-lined REMS document, REMS materials, and REMS Supporting Document are based on the Agency's review of these submissions. Please note that comments on these documents are preliminary and may be revised over the course of the review.

In order to facilitate further review, we ask that you respond to these comments within 10 business days.

I. REMS Document

Your proposed REMS document follows the draft guidance for Industry Format and Content of the REMS; however, additional edits are necessary to align with the REMS template to support standardization of the format and content of REMS. In addition, the REMS and all the REMS materials will need to align with final labeling.

A summary of the significant additions and deletions are listed below.

1) In general, we agree with your proposed REMS goals with some modifications.

The 1st goal has been revised to include, "adhere" and the requirement of submission of documentation has been added to the goal.

A (b) (4) is not a proposed element of the REMS; therefore, a separate goal is necessary. (b) (4)

2) In section III.1. Before treatment initiation (first dose), item 7 was added and 8 was changed in this section of the document. See text below to the following:

> 7. Assess the patient's ocular health by consulting an eye care professional to complete visual acuity and slit lamp using the Eye Care Professional Consult Request Form.
>
> 8. Assess the patient's ophthalmologic consult results for appropriateness of initiating treatment. Document and submit to the REMS Program using the Patient Status Form.

3) Text was inserted in section III.1. During treatment; before each infusion, items 9 and 10 were added.

4) We do not agree with your proposal (b) (4) The patient will be provided a Patient Guide that support awareness and education of risk of ocular toxicity, and thus the (b) (4) is redundant.

5) The title has been revised in section III.3. for clarity and to ensure consistency with other REMS programs as well as to align with the draft guidance for industry- Format and Content of a REMS Document.

6) In order to reduce burden on stakeholders we recommend removing (b) (4) (b) (4) and revise the language as outlined below in section III.3. To maintain certification to dispense.9:

> 9. Have the authorized representative enroll in the REMS Program by completing and submitting the Healthcare Setting Enrollment Form to the REMS program.

7) Since wholesalers-distributors are involved in the process of distribution of Blenrep to certified healthcare settings, they must be covered in the REMS document. wholesalers-distributors and must only distribute to certified healthcare settings.

8) [redacted] (b) (4) REMS Letters should target the healthcare providers, likely to prescribe, dispense or administer Blenrep.

9) The [redacted] (b) (4) are not necessary. [redacted] (b) (4)

10) Changes are needed to the implementation system for it to be acceptable. We have inserted the language in regards of database accessibility. Provide the processes and procedures for prescribers to access the database of certified healthcare settings and their enrolled patients. You must also provide authorized wholesalers-distributors access to the database of certified healthcare settings. Please include details in your REMS Supporting Document.

11) In the section, To support REMS Program operations, GlaxoSmithKline must, we have added the following language to support REMS Program operations.

    1. Authorize dispensing for each patient based on receipt of the Patient Enrollment Form and Patient Status Form on the following schedule: Authorize the first patient shipment upon receipt of the Patient Enrollment Form and Patient Status Form. If a completed Patient Enrollment Form and Patient Status Form are not received, the patient is not authorized to receive drug. For subsequent dispensing, if the Patient Status Form is not received [insert timeframe], the patient is not authorized to receive drug.

    7. Ensure prescribers are able to use the Eye Care Professional Consult Request Form by fax and with healthcare software.

12) In the section, To ensure REMS participants' compliance with the REMS program, GlaxoSmithKline must, we have added the following language to ensure compliance with the REMS program.

    [redacted] (b) (4) if the Patient Status Form is not received [insert timeframe], the patient is not authorized to receive subsequent drug shipments

13) The [redacted] (b) (4) are not part of REMS, and should not be included in the REMS.

II. REMS Supporting Document

Align the REMS Supporting Document with the REMS Document and label. It is not clear how the drug is distributed to the Healthcare Setting. Provide the information whether the drug only shipped to the Healthcare Setting for a specific patient or is stocked.

REMS Assessment Plan

Assessment Plan Comments:

- Refer to the draft guidance "Survey Methodologies to Assess REMS Goals That Relate to Knowledge: Guidance for Industry" released in January 2019 for further guidance on conducting REMS assessment surveys including study design, survey instrument development, sampling, survey data collection and processing, and data analysis. You propose a knowledge survey to evaluate healthcare provider's understanding of the corneal adverse reactions associated with Blenrep and the need to counsel patients regarding the risk and the need for baseline and regular ophthalmic exams. Discuss the feasibility of conducting a survey in this population and provide the rationale for using 80% as the target level for comprehension. Include the estimated size of the healthcare provider population for each year in the next 7 years. If a survey is not feasible, include other approaches to evaluate knowledge.
- For the Communication Plan, include metrics to measure the extent to which the REMS materials reached the intended stakeholders.
- Refer to the draft guidance "REMS Assessment: Planning and Reporting" released in January 2019 for further guidance on developing and formatting an assessment plan. Provide a table that outlines how each of the objectives of the goal will be met. See example in Appendix A in the last page.

Audit/Compliance Protocols:

- Submit an audit protocol as an appendix to the REMS Supporting Document that includes, but not limited to: objective and scope of the audits, methods used for audits, and types of corrective actions that may be taken to address noncompliance.
- You noted that a plan will be established for addressing noncompliance with the REMS program requirements. Explain this plan, including, but not limited to: (b) (4) (b) (4) the scope and clear definitions of non-compliance examples, and actions that may be taken to correct and prevent future occurrences (e.g. warnings, suspension, deactivation, recertification). Submit a non-compliance protocol as an appendix to the REMS Supporting Document.

III. REMS Materials:

General Comments:

Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features. If your logo states BLENREP REMS, you do not need to repeat the name BLENREP REMS in the title of all your communication materials.

The formatting for forms should have a consistent style and construction. Replace triangle bullets with simple closed circles. The second line of bullets should have the margin flush with text from first line, not the bullet. Headings should be formatted so that they provide visual distinction between sections. Consider included small white space in between sections similarly to the Healthcare Setting Enrollment Form.

All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.

All REMS program information must reflect what is in the REMS Document. Make any changes in the materials to be included in your next submission.

Phone numbers used by the Blenrep REMS may not link to information that is promotional in tone.

We have provided redlined documents, or other edited formats for each of the documents below.

Healthcare Providers REMS Letter

We have made edits to be more concise. The REMS Document states that the initial letter will be an email. Please submit the formatted email version of the letter.

REMS Letter for Professional Societies

We have made edits to be more concise.

Factsheet

Graphics can be difficult to use as they may cause more confusion rather than be a helpful visual association. Although we can appreciate the graphics and color, the second page looks really busy. Replace the green graphics on this page with simple bullets, like a closed circle. We also recommend replacing the orange font for the materials with black font. Left justify font size 11 instead of 12, if more space is needed to incorporate changes.

The risk messaging in the Factsheet must align with the label.

Program Overview

There is a lot of text in this document. To make this easier to read, incorporate formatting such as color, text columns, a unique color scheme for each audience and/ or some other formatting designs to break up the text and make the document more user friendly. Please look to other REMS Overviews, such as Turalio, Tegsedi, or Palinziq to see examples of incorporating formatting design changes to present a lot of information.

We made minor edits to the risk information and removed redundant information.

Patient Enrollment Form

Formatting for this form should like other forms, such as the Healthcare Setting Enrollment Form. For example, headings (Patient Information, Prescriber Information) could be in dark text on lighter background to stand out visually. Include white space to visually separate each section.
Replace triangle bullets with something simple like closed circles. Please note that the attestations are still under review and could be subject to change.

Patient Guide

We have made edits to provide concise information related to the risk of ocular toxicity and the requirements of the BLENREP REMS.

Prescriber Enrollment Form

Use consistent formatting across forms. This form has data fields spread out. Consider putting inboxes.

We have removed background information from this form. Please note that the attestations are still under review and could be subject to change.

(b) (4)

We have removed redundant information. More context showing the step to obtain authorization to administer each dose of BLENREP is needed, along with each verification step. The two forms ((b) (4) Checklist and Patient Status Form) and required actions regarding the forms are not presented clearly. Consider putting in a slide on the website portal, as that is a tool that can be used by the healthcare setting staff.

Healthcare Setting Enrollment Form

Remove the section (b) (4)

Attestations are going through review and may change.

Website desktop/ mobile

Consider using title case for green headings since they are a bit longer and the ALL CAPS is more difficult to read.

The (b) (4) can be removed from the website landing page. This information is contained in the REMS details provided on subsequent pages.

Apply our comments on the REMS materials to similar presentations in the REMS Website Desktop and Mobile screenshots. Final website screenshots should also incorporate these changes.

Submit a complete set of updated REMS website screenshots showing all content and functionality of the website. Since online education and enrollment is an option, you must submit a screenshot(s) of what the new window(s) would look like as part of the functionality of your website submission. This would include the data fields to complete, and the information that pops up for the provider to read.

Your proposed BLENREP website portal allows for real-time access to BLENREP REMS patient, prescriber, and healthcare setting information. The website portal is considered a part of the BLENREP REMS. We

must review all screenshots showing the functionality of the portal. Submit screenshots for the website portal.

Other REMS Materials

The following materials in the REMS Document are still undergoing internal review: Patient Status Form, Eye Care Professional Consult Request Form, (b) (4) Prescriber Knowledge Assessment, (b) (4) Checklist. Comments will be forthcoming.

Non-REMS Material

We do not agree with the proposal (b) (4)
however, these materials should not be included in the REMS. We do not agree with the proposal (b) (4) (b) (4) Submit these materials to The Office of Prescription Drug Promotion (OPDP) in compliance with the advertising and marketing regulations.

Resubmission Instructions

Submit the following revised REMS materials to your application by **July 10, 2020**. The next submission to the Gateway should include Clean MS Word, Tracked MS Word (if applicable), and final formatted pdf or PowerPoint versions of the following documents:

- **BLENREP REMS Document**
- **BLENREP REMS Supporting Document**
- **BLENREP REMS Materials**

Appendix A. Example of a Partial Assessment Plan Table

Goals and objectives	Assessment Plan Category	Requirements	REMS materials	Metrics	Data Sources or Analytical Tools	REMS Assessment Report: Frequency of Metric Reporting	Performance Threshold	Methodology/Protocol Location and Date Submitted
Goal: Mitigate the risk of corneal adverse reactions	Health Outcomes	Safety Surveillance	TBD	• Adverse events of corneal adverse reactions	TBD	TBD	TBD	TBD
Objective 4: Enrollment of all patients into the Blenrep REMS	Implementation and Operations	Enrollment Data	• Patient Enrollment Form	• Number of newly enrolled patients • Total number of patients currently enrolled at the end of the reporting period	• REMS database	Annual reports	None	TBD
	Implementation and Operations	Compliance Data	• (b) (4) Checklist	• Number of patients who were not enrolled at the time of administration	• REMS database • Audits Findings	Annual reports	>XX% of patients must be enrolled prior to receiving Blenrep	• Compliance protocol [submitted on date] • Audit protocol [submitted on date]

65 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
06/26/2020 01:10:29 AM

KATE H OSWELL
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CAROLYN N TIEU
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NAOMI S BOSTON
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CYNTHIA L LACIVITA
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