U.S. FOOD & DRUG ADMINISTRATION

BLA 761158

GENERAL ADVICE

GlaxoSmithKline Intellectual Property Development Ltd. England
Attention: Concetta Freund, MS
Director, Oncology Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Freund:

Please refer to your biologics license application (BLA) dated December 5, 2019, received December 5, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Blenrep (belantamab mafodotin-blmf) for injection.

We reference your BLA Accelerated Approval Letter issued on August 5, 2020. Below is the additional manufacturing information.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture belantamab drug substance intermediate at Human Genome Sciences in Rockville, MD and the belantamab mafodotin drug substance at (b) (4) The final formulated product will be manufactured and filled at (b) (4) and labeled and packaged at GlaxoSmithKline Manufacturing SpA, Parma, Italy. You may label your product with the proprietary name Blenrep and will market it in 100 mg / Powder for Injection.

If you have any questions, call Wanda Nguyen, PharmD, Regulatory Project Manager, at (301) 796-2808.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director (Acting)
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research (CDER)

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/

NICOLE J GORMLEY
08/07/2020 06:56:14 PM

BLA 761158

BLA ACCELERATED APPROVAL

GlaxoSmithKline Intellectual Property Development Ltd. England
Attention: Concetta Freund, MS
Director, Oncology Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Freund:

Please refer to your biologics license application (BLA) dated December 5, 2019, received December 5, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Blenrep (belantamab mafodotin-blmf) for injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2148 to GlaxoSmithKline Intellectual Property Development Ltd. England, Brentford, Middlesex, United Kingdom, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Blenrep (belantamab mafodotin-blmf). Blenrep is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture belantamab drug substance intermediate at Human Genome Sciences in Rockville, MD and the belantamab mafodotin drug substance at (b) (4) The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) (b) (4) You may label your product with the proprietary name Blenrep and will market it in 100 mg / Powder for Injection.

DATING PERIOD

The dating period for Blenrep shall be 12 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance intermediate shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4) °C The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Blenrep to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Blenrep, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on July 7, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761158**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2020. This requirement, along with required completion dates, is listed below.

3800-1 Submit the final study report and datasets from a randomized phase 3 clinical trial that verifies and describes the clinical benefit of belantamab mafodotin in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive belantamab mafodotin compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints that include overall survival and overall response rate, as well as patient-reported outcomes. This trial should include a sufficient number of older patients (ages 65-74 and ≥75) and patients with extramedullary disease.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Draft Protocol Submission: 04/2020 (completed)
Final Protocol Submission: 09/2020
Trial Completion: 09/2022
Final Report Submission: 01/2023

Submit clinical protocols to your IND 119333 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of ocular toxicity in patients receiving belantamab mafodotin-blmf.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3800-2 Conduct 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 final report containing data from this study, other clinical trials and other sources to further characterize the mechanisms by which belantamab mafodotin causes ocular toxicity.

Draft Protocol Submission:	05/2021
Final Protocol Submission:	03/2022
Study Completion:	09/2022
Final Report Submission:	03/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to characterize the safety and determine appropriate dose adjustment in the lyophilized presentation of belantamab mafodotin; to assess a known risk of ocular toxicity; to identify an unexpected serious risk of elevated drug levels in the presence of moderate or severe hepatic impairment, severe renal impairment and end-stage renal disease; and to establish the relationship between cys-mcMMAF exposure and safety events.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3800-3 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. Provide the datasets with the final study report.

The timetable you submitted on August 4, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	06/2022
Interim Report Submission:	01/2023
Study Completion:	05/2025
Final Report Submission:	11/2025

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3800-4 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. The study's primary objective is to assess the ocular toxicity in all treatment arms with efficacy and PK evaluations as secondary objectives. The results of this trial may inform product labeling. Submit a final report with full datasets.

The timetable you submitted on August 4, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2021
Final Protocol Submission:	09/2021
Trial Completion:	04/2025
Final Report Submission:	10/2025

3800-5 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. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling"

The timetable you submitted on August 4, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2019 (completed)
Final Protocol Submission:	03/2020 (completed)
Trial Completion:	01/2025
Final Report Submission:	07/2025

3800-6 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. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Pharmacokinetics in Patients with Impaired Renal

Function — Study Design, Data Analysis, and Impact on Dosing and Labeling"

The timetable you submitted on August 4, 2020 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2019 (completed)
Final Protocol Submission:	03/2020 (completed)
Trial Completion:	11/2025
Final Report Submission:	05/2026

3800-7 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. Support this study by updating and submitting the final report of the clinical pharmacology analysis, that was previously submitted to this BLA, including updated noncompartmental analyses, population pharmacokinetic, exposure-response analyses for efficacy and safety, concentration-QT analyses.

The timetable you submitted on August 4, 2020, states that you will conduct this trial according to the following schedule:

Stability Report Submission:	03/2021
Final Report Submission (updated BLA reports):	09/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocols to your IND 119333 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3800-8 Submit an integrated final report and datasets from clinical trials to further characterize the efficacy of belantamab mafodotin in patients with extramedullary disease. The report should include the rates of overall response and overall survival.

The timetable you submitted on August 4, 2020, states that you will conduct this study according to the following schedule:

Draft protocol Submission: 05/2021
Final Protocol Submission: 03/2022
Trial Completion: 09/2022
Final Report Submission: 03/2023

3800-9 Submit an interim and a final integrated report containing data from clinical trials and other data sources such as, expanded access treatment protocols, post marketing reports and real world data, to further characterize the ocular toxicity, including keratopathy, changes in visual acuity, and other ocular symptoms with belantamab mafodotin in older age subgroups of patients, age 65-74 years and ≥75 years, with relapsed or refractory multiple myeloma, compared to patients <65 years. The study report should also include the overall response rate and overall survival in the older age subgroups compared to patients <65 years to provide longer-term data to further characterize the benefit-risk profile in older age subgroups. The results from this study may inform product labeling.

The timetable you submitted on August 4, 2020, states that you will conduct this study according to the following schedule:

Draft protocol Submission: 09/2021
Final Protocol Submission: 09/2022
Trial Completion: 03/2023
Final Report Submission: 01/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 119333 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

ENHANCED PHARMACOVIGILANCE MONITORING

For a period of 5 years from the U.S. approval date, 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)). Provide detailed analyses of ocular toxicity reported from clinical study and postmarketing reports in the periodic safety report, including case narratives of changes in visual acuity to worse than 20/200, complete vision loss, corneal ulcers, and corneal transplants, with the following information in table format: demographics, predisposing risk factors/comorbidities, signs, symptoms, relevant laboratory data/examination leading to diagnosis, and re-challenge/de-challenge information. The analyses should show cumulative data relative to the date of approval of belantamab mafodotin as well as relative to the prior periodic safety reports. Medical literature reviews for case reports/case series of ocular toxicity reported with belantamab mafodotin should also be provided in the periodic safety report.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Blenrep (belantamab mafodotin-blmf) to ensure the benefits of the drug outweigh the risk of ocular toxicity.

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Blenrep (belantamab mafodotin-blmf) will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about the risk of severe ocular toxicity, as well as the requirements for prescriber certification, pharmacy or healthcare setting certification, documentation of safe use, and patient monitoring requirements.

The communication plan must include, at minimum, the following:

- REMS Letter to Healthcare Providers and Professional Societies
- REMS Factsheet
- Dissemination of the REMS Factsheet through field-based sales and medical representatives for 12 months after Blenrep is first commercially distributed

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Blenrep (belantamab mafodotin-blmf) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of ocular toxicity listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

- Each patient using the drug is subject to certain monitoring

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on August 5, 2020, amended and appended to this letter, is approved.

The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Blenrep (belantamab mafodotin-blmf) into interstate commerce.

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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761158 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761158 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761158/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761158/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761158/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761158/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761158

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain

documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Wanda Nguyen, PharmD, Regulatory Project Manager, at 301-796-2808.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Acting Deputy Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

MARC R THEORET
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