BLA 761032/S-008

SUPPLEMENT APPROVAL

Bausch Health Ireland, Limited
C/o: Bausch Health US, LLC
Attention: Libette Luce, MA
Senior Director, Global Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Luce:

Please refer to your supplemental biologics license application (sBLA), dated and received July 29, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Siliq (brodalumab).

This Prior Approval supplemental biologics application provides for proposed modification to the approved Siliq risk evaluation and mitigation strategy (REMS). This supplement is in response to our April 9, 2020, REMS Modification Notification letter.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Siliq (brodalumab) was originally approved on February 15, 2017, and the most recent REMS modification was approved on October 9, 2018. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to ensure the benefits of Siliq outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated April 9, 2020. In addition, the following modifications were communicated during the course of the review:

- Conversion of the REMS Document to the new, standardized format
- Removal of the word “Program” from the titles of the REMS materials to reflect current practice on naming
- Changes to the *Stakeholder Enrollment Form* instructions to improve clarity and removal of the DEA field as brodalumab is not a controlled substance
- Changes to the *Patient Enrollment Form* to expand the gender categories to improve inclusivity
- Changes to the REMS materials to align with changes to the REMS Document

Your proposed modified REMS, submitted on July 29, 2020, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on February 15, 2017.

. We have determined that your REMS assessment plan requires revision to address minor editorial discrepancies. The revised REMS assessment plan must include, but is not limited to, the following:

1. **SILIQ Stakeholder data** (prescribers, pharmacies, patients, and wholesalers-distributors) per reporting period and cumulatively:
   a. Number of certified/enrolled stakeholders, status of certification, and method of certification including:
      i. Number of certified prescribers by medical degree, geographic location, prescriber specialty, method of certification (email, fax, online), and the number and percentage of enrolled health care providers who have prescribed SILIQ.
      ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient) and method of certification (email, fax, online).
      iii. Number of authorized distributors and wholesalers.
      iv. Number of enrolled patients and their demographics (age, gender, race, geographic location).
   b. Listing and categorization of reasons when enrollment is incomplete for each stakeholder category.

2. **Utilization Data,** per reporting period and cumulatively: Number of SILIQ prescriptions (new and refills) dispensed stratified by:
   a. pharmacy type
   b. method of dispensing authorization (on-line versus phone)
   c. prescriber specialty
   d. patient demographics (age, race, gender)

3. **Compliance Metrics,** per reporting period and cumulatively**:**
   a. A copy of the audit plan for each stakeholder (certified pharmacies, distributors, and prescribers).
   b. A copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event led to de-certification from the REMS.
   c. Report of audit findings for each stakeholder including:

i. The number of audits expected, and the number of audits performed.

ii. The number and types of deficiencies noted for each group of audit stakeholders.

iii. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan.

iv. For any that did not complete the CAPA, describe actions taken.

v. Include a unique ID for each stakeholder that has had deviations to track deviations by stakeholder over time.

vi. Documentation of completion of training for relevant staff.

vii. The existence of documented processes and procedures for complying with the REMS.

viii. Verification that each audited stakeholder's site has retained the same designated authorized representative. If different, include the number of new authorized representative and verification of the site's recertification.

d. Report of annual audit findings from wholesalers-distributors for audits conducted during the reporting period, including:
   i. What processes and procedures the REMS and wholesalers-distributors have in place to verify, prior to dispensing SILIQ, that the pharmacies are certified. This report is to include the source of the report, a description of the event, the root cause analysis of any findings of non-compliance, any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken.

e. Report of audit findings from the certified pharmacies that have dispensed SILIQ
   i. This report is to include the source of the report, a description of the event, the root cause analysis of any findings of non-compliance, any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken.

f. Report of findings from audit of the pilot prescription program specialty pharmacy
   i. This report is to include the source of the report, a description of the event, the root cause analysis of any findings of non-compliance, and any resulting preventative actions taken.

g. Number of SILIQ prescriptions dispensed that were written by non-certified prescribers, the root cause analysis of dispensing a prescription by a non-certified prescriber, whether the patients were enrolled or not enrolled, and the actions taken to prevent future occurrences. Include a unique ID for each pharmacy to track deviations over time.

h. Number of SILIQ prescriptions that were dispensed to non-enrolled patients, the root cause analysis of dispensing a prescription to a non-enrolled patient, whether the prescriber was certified or non-certified, and the actions taken to prevent future occurrences. Include a unique ID for each pharmacy to track deviations over time.

i. Number of SILIQ prescriptions dispensed by non-certified pharmacies, the root cause analysis of how a non-certified pharmacy obtained SILIQ, and the actions taken to prevent future occurrences.

j. Number of times a SILIQ prescription was dispensed because a certified pharmacy bypassed the REMS authorization process, the root causes analysis of why the pharmacy bypassed the REMS authorization process; to include a description of how the events were identified and any corrective actions taken.

k. Number of shipments sent to non-certified pharmacies, the root cause analysis of shipping to a non-certified pharmacy, sources of the reports, and actions taken to prevent future occurrences.

l. Number of prescribers, pharmacies, and distributors de-certified and reasons for decertification.

m. The number of and reasons for rejected prescription authorizations.

n. Failures of prescription dispensing authorization due to calls to the REMS for authorization when the call center was closed or when the prescriber/patient verification portion of the website was down.

o. The numbers of the most frequently asked questions to the Call Center organized by topic.

4. **Evaluation of knowledge via Knowledge, Attitude and Behavior (KAB) surveys**

a. Prescribers

i. An evaluation of knowledge of certified prescribers of the potential risk of suicidal ideation and behavior observed with SILIQ therapy.

ii. An evaluation of prescriber practice or behavior with regards to counseling patients about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of certified prescriber knowledge of SILIQ REMS requirements and processes.

b. Patients

i. An evaluation of knowledge of patients of the potential risk of suicidal ideation and behavior observed with SILIQ therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the potential risk of suicidal ideation and behavior observed with SILIQ therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.
iii. An evaluation of patient receipt of the wallet card.

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 1 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) of the FDCA. 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 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 that 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 REMS modifications, 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 761032 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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 761032 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761032/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/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 761032/ 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 REVISIONS FOR BLA

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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.

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 none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Dawn Williams, Safety Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- 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/

TATIANA OUSSOVA
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