DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 0761032/S-005

SUPPLEMENT APPROVAL

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
Attention: Isabelle Lefebvre
Vice President Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Ms. Lefebvre:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received August 10, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Siliq (brodalumab).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 15, 2018.

This "Changes Being Effected" supplemental biologics application provides for modifications to the approved risk evaluation and mitigation strategy (REMS).

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 January 26, 2018. The REMS consists of elements to ensure safe use, an implementation system, and a timetable of submission of assessments of the REMS. Your proposed modifications to the REMS consist of: removal of the Website Consent section of the *SILIQ REMS Program Prescriber Enrollment Form* by which prescribers authorize the publishing of their information on the REMS website, and removal of the listing of certified prescribers from the REMS website. In addition, this approval also incorporates a change to the Siliq REMS Program assessment audit plan based on a change to Valeant's certified pharmacy operations.

Your proposed modified REMS, submitted on August 10, 2018, amended and appended to this letter, is approved.

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

There are changes to the REMS assessment plan that was approved in our August 27, 2018 REMS Assessment Acknowledgement/ REMS Assessment Plan Revision letter. The new assessment plan is as follows:

REMS ASSESSMENT PLAN

1. **SILIQ Stakeholder data** (prescribers, pharmacies, patients, and distributors/wholesalers) per reporting period and cumulatively:
   a. Numbers of each certified/enrolled stakeholder, status of certification, and method of certification including:
      i. Number of certified prescribers by medical degree, geographic location, prescriber specialty, and method of certification (email, fax, online); the number and percentage of enrolled health care providers who have prescribed Siliq
      ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient chain, outpatient independent) 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**:**
   a. Report of annual audit findings from a representative sample of 25% wholesaler/distributors or one, whichever is greater, for audits conducted during the reporting period, including:
      i. What processes and procedures the REMS and distributors/wholesalers have in place to verify, prior to dispensing SILIQ, that the pharmacies are certified
      ii. Any corrective actions taken to address findings of non-compliance
      iii. The status of corrective actions,
      iv. Any resulting preventative actions taken.
   b. Report of findings from an audit of 20% of the certified pharmacies that have dispensed Siliq or one, whichever is greater, within 90 calendar days after the pharmacy places its first order of SILIQ to ensure that all processes and procedures are in place and functioning
      i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken

c. Report of findings from audit of the pilot prescription program specialty pharmacy within 90 calendar days after the pharmacy places its first order of Siliq to ensure that all processes and procedures are in place and functioning
    i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken

d. Number of SILIQ prescriptions dispensed that were written by non-certified prescribers, the number of those prescriptions that were dispensed, and the actions taken to prevent future occurrences.

e. Number of SILIQ prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.

f. Number of times a SILIQ prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.

g. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.

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

i. The number of and reasons for rejected prescription authorizations

j. Failures of Rx 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

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

l. Siliq REMS Patient-Prescriber Acknowledgement Form
    i. Total number and percentage of enrolled patients who had a complete, signed, Siliq REMS Patient-Prescriber Acknowledgment Form on record versus those who did not.
    ii. Total number and percentage of patients who had a Siliq prescription dispensed who had a complete, signed Siliq REMS Patient-Prescriber Acknowledgment Form on record versus those who did not.

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 0761032 REMS ASSESSMENT METHODOLOGY

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 0761032 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 0761032/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 0761032/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 0761032/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 0761032/ 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 0761032

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, 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 Dental Products
Office of Drug Evaluation III
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
10/09/2018