CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761032Orig1s000

Trade Name: Siliq

Generic Name: brodalumab

Sponsor: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

Approval Date: February 15, 2017

Indications: Indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761032Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

BLA APPROVAL

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Siliq (brodalumab).

We also refer to our approval letter dated February 15, 2017 which contained the following errors:

- The dating period for Siliq shall be 12 months from the date of manufacture when stored at 2-8°C.
- The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4).

This replacement approval letter incorporates the corrections of the errors. The effective approval date will remain February 15, 2017, the date of the original approval letter.

We acknowledge receipt of your major amendment dated October 18, 2016, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2053 to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL), Grand Duchy of Luxembourg, Luxembourg, 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 Siliq (brodalumab). Siliq is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture brodalumab drug substance at (b) (4) (b) (4). The 210 mg/1.5 mL drug product will be manufactured at (b) (4), and packaged and labeled at (b) (4) (b) (4). You may label your product with the proprietary name, Siliq, and market it in a 210 mg/1.5 mL pre-filled syringe.

DATING PERIOD

The dating period for Siliq shall be 24 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 shall be (b) (4) months from the date of manufacture when stored at (b) (4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating periods of your drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Siliq 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 Siliq, 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 & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide and Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on December 13, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761032**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

We are waiving the pediatric study requirement for ages < 6 years because necessary studies are impossible or highly impracticable. This is because the prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest published prevalence of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

We are deferring submission of your pediatric studies for ages 6 to <18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Based on the immunomodulatory mechanism of action for brodalumab, pediatric studies in population 6-17 years of age with moderate to severe psoriasis will likely be deferred at least until after adult studies have been completed and a determination of safety and efficacy has been made for adult psoriasis subjects.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

3164-1 Open-label study to determine PK of a single dose of brodalumab in 16 children (6 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission: 06/17
Study Completion: 01/19
Final Report Submission: 06/19

3164-2 Double-blind, active comparator-controlled, multicenter study with brodalumab to determine the safety and efficacy in adolescent subjects (12 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission: 04/19
Study Completion: 01/24
Final Report Submission: 06/24

3164-3 Open label, single arm study with brodalumab to determine safety and efficacy in children (6 to <12) with severe plaque psoriasis.

Final Protocol Submission: 04/24
Study Completion: 01/29
Final Report Submission: 06/29

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 identify an unexpected serious risk of maternal, fetal and neonatal toxicity as well as an unexpected serious risk of malignancy, opportunistic infections, and neutropenia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

3164-4 Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women with a diagnosis of psoriasis exposed to brodalumab versus a non-brodalumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	12/22
Final Report Submission:	06/23

3164-5 Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women with the diagnosis of psoriasis exposed to brodalumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	06/30
Final Report Submission:	06/31

3164-6 Conduct a prospective, observational study to assess the long-term safety of Siliq (brodalumab) compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB], opportunistic mycoses) and neutropenia. Describe and justify the choice of appropriate comparator population(s) and

estimated background rate(s) relative to brodalumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the brodalumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period, including any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

The timetable you submitted on December 23, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	08/17
Final Protocol Submission:	03/18
Study Completion:	11/30
Final Report Submission:	11/31

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA. Submit 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 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 NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3164-7 Submit final study report for LC/UV/MS analysis using appropriate control samples to confirm the capability of this method to detect volatile compounds in the presence of brodalumab drug product.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/17

Submit 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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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 [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Siliq (brodalumab) to ensure the benefits of the drug outweigh the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Siliq (brodalumab) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq that is listed in the labeling. The elements to assure safe use (ETASU) are intended to ensure that prescribers are informed about the risk of SIB observed with Siliq therapy and the need to counsel patients about this risk. The ETASU are also intended to ensure that patients are informed about the risk of SIB observed with Siliq therapy and the need to seek medical attention should they experience manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers who prescribe must be specially certified.
- Pharmacies that dispense the drug are specially certified.

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

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified, and the drug be dispensed to patients with documentation of safe-use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on February 13, 2017, and appended to this letter, is approved.

The REMS consists of 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 Siliq (brodalumab) into interstate commerce.

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

1. Siliq Stakeholder data (prescribers, pharmacies, patients, and distributors) 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, prescriber specialty, and method of certification (email, fax, online)
        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)
    b. Listing and categorization of reasons 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, gender, race)
3. Compliance Metrics, per reporting period**:**

a. Report of annual audit findings from a representative sample of 25% of certified pharmacies 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 25% of the certified pharmacies 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. Number of Siliq prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.
d. Number of Siliq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
e. 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.
f. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.
g. Number of prescribers, pharmacies and distributors de-certified and reasons for decertification.
h. The number of and reasons for rejected prescription authorizations.
i. 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.
j. The numbers of the most frequently asked questions to the Call Center organized by topic.

4. REMS Program implementation (to be provided in the 12 month assessment only)
    a. Product Launch Date
    b. Date when the Siliq REMS website went live
    c. Date healthcare providers could become certified online, by email, or by fax

d. Date when the REMS Program Website & Call Center are fully operational, including the online confirmation of patient authorization functionality and the availability of REMS materials

5. 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.
   c. Pharmacies
      i. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies 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 knowledge of authorized representatives and staff pharmacists in certified pharmacies of the Siliq REMS requirements and processes.

6. 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 (Section 505-1(g)(3).

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 761032 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,

UPDATE TO REMS SUPPORTING DOCUMENT - 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 761032 REMS ASSESSMENT

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 LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

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 REVISION FOR BLA 761032

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.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 REMS_Website@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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 4206
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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

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.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA

approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
- Carton and Container Labeling
- REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
02/15/2017