



BLA 125166/S-427
BLA 125166/S-428

**SUPPLEMENT APPROVAL
REMS MODIFICATION**

Alexion Pharmaceuticals, Inc.
Attention: Mary F. Lyons, RAC
Associate Director, Regulatory Affairs
121 Seaport Boulevard
Boston, MA 02210

Dear Ms. Lyons:

Please refer to your two Supplemental Biologics License Applications (sBLAs), dated March 5, 2018, received March 5, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Soliris (eculizumab) injection, 300 mg/30 mL (10 mg/mL).

Prior Approval supplemental biologics application 427 provides for updates to U.S. Prescribing Information (PI) in the Boxed Warning, Section 2 DOSAGE AND ADMINISTRATION, Section 5 WARNINGS AND PRECAUTIONS, and Section 7 DRUG INTERACTIONS.

Prior Approval supplemental biologics application 428 provides for the following modifications to the approved risk evaluation and mitigation strategy (REMS) for Soliris (eculizumab): modifications to the REMS Program supporting document, Soliris REMS document, Prescriber Safety Brochure, REMS Dosing and Administration guide, and Prescriber Introductory Letter and Enrollment Form, and removal of the Medication Guide from the REMS.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. Both are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. 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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

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

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.

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Soliris (eculizumab) was originally approved on June 4, 2010, and the most recent REMS modification was approved on October 23, 2017. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of modifications to the REMS Program supporting document, Soliris REMS document, Prescriber Safety Brochure, REMS Dosing and Administration guide, and Prescriber Introductory Letter and Enrollment Form, and removal of the Medication Guide from the REMS.

In order 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 email dated December 6, 2017.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Soliris outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on March 5, 2018, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, 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 April 30, 2014.

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

1. Prescriber Enrollment:
 - a. Numbers enrolled: total and newly enrolled during the reporting period
 - b. Number who are prescribing Soliris who are not enrolled
 - c. Specific reasons that prescribers did not enroll
 - d. Actions taken to ensure that no prescriber who is not enrolled is allowed to prescribe Soliris and that all prescribers of Soliris are enrolled
 - e. Root causes analyses of instances where non-enrolled prescribers were distributed Soliris (especially those cases where more than one distribution was made to an unenrolled prescriber)
 - f. Actions taken to ensure that all prescribers are enrolled
2. Patient statistics:
 - a. The number of new patients treated with Soliris for the annual reporting period and cumulatively
 - b. Demographics of patients treated with Soliris (gender, pediatric age group, diagnosis) for the reporting period and cumulatively
 - c. Number of new patients treated with Soliris receiving meningococcal vaccination according to current ACIP recommendations for persons who have complement deficiency for the reporting period and cumulatively. Information regarding the vaccines administered is to include vaccine serotype, dosing, and timing of the vaccinations.

3. Summary of cases of U.S. meningococcal infections
 - a. Summarize cases for the following timeframes:
 - i. During the current reporting period in the most recent PSUR submitted to the Soliris BLA with a link to that PSUR identified
 - ii. Cumulative listing of all U.S. cases of meningococcal infections from approval (including cases reported 2007 – 2010) to include cases identified during the current reporting period
 - b. For each case, provide the following information:
 - i. MedWatch or other case report number
 - ii. date of report and date of report to FDA
 - iii. age and gender
 - iv. indication for Soliris treatment
 - v. meningococcal vaccination status, including whether vaccinations were administered in compliance with the most current ACIP recommendations with regards to vaccine product, dosage, and timing
 - vi. whether the patient was administered any prophylactic antibiotics and if so:
 1. the specific antibiotics, antibiotic regimen (dose/frequency), and routes of administration
 2. the duration of the antibiotic treatment
 3. the timing of the course of the antibiotics in relation to Soliris treatment
 - vii. summary of the clinical course and the outcome
 - viii. causative meningococcal serogroup
 - ix. whether the Patient Safety Information card was presented during the process of the patient seeking treatment
4. Rate (# cases/100,000 patient-years) of meningococcal infections for the reporting period; rates for U.S. cases, worldwide cases and relevant age subgroups (ages 0-18 years, 18-55 years, and >55 years) are to be calculated and provided. Include rates for each year since approval of Soliris.
5. An assessment of prescriber and patient understanding regarding the safe use of Soliris, i.e., the results of separate surveys administered to prescribers and patients. This will include the basic demographics of participating patients (age, gender) and participating prescribers (specialty, number of patients being treated with Soliris).
6. 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 125166 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 125166 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR BLA 125166/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125166/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125166/ 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 125166/ 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 125166

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.

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 prescribing information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, 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>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax

to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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 Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277 or Diane Leaman, Safety Regulatory Project Manager at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Barry W. Miller
Acting Deputy Division Director, Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling
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/

BARRY W MILLER
07/25/2018