BLA 125166/S-432

SUPPLEMENT APPROVAL

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

Dear Ms. Lyons:

Please refer to your supplemental biologics license application (sBLA), dated and received February 11, 2020, submitted under section 351(a) of the Public Health Service Act for Soliris® (eculizumab) Sterile Parenteral Solution for IV infusion, 300 mg (10 mg/mL).

This Changes Being Effected supplemental biologics license application provides for proposed modifications to the approved Soliris® 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 Soliris® was originally approved on June 4, 2010, and the most recent REMS modification was approved on June 27, 2019. The REMS consists of elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of revisions to the Prescriber Enrollment Form to include prescriber specialty.

Your proposed modified REMS, submitted on February 11, 2020, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on April 30, 2014.

Our March 10, 2020, REMS Assessment Acknowledgment/REMS Assessment Plan Revision letter described your REMS assessment plan. We have determined that your

REMS assessment plan needs revision to capture healthcare provider medical specialty in the Healthcare Provider Enrollment metric.

Within 60 days of receipt of this letter, submit an updated supporting document that incorporates the revised assessment plan. Additions are noted by underline and deletions are noted by ~~strikethrough~~.

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

Program Implementation and Operations:

1. ~~Prescriber~~ Healthcare Provider Enrollment (per reporting period and cumulatively):
    a. Numbers enrolled: total, newly enrolled, and active (ordered Soliris at least once during the reporting period) stratified by medical specialty

2. Patient statistics (per reporting period and cumulatively):
    a. The number of new patients treated with Soliris
    b. Demographics of patients treated with Soliris (gender, pediatric age group, diagnosis)
    c. A comparison of the number of patients who received Soliris to the number of patients enrolled in the voluntary patient support program

3. REMS Compliance (per reporting period and cumulatively)
    a. Provide a summary of non-compliance identified, including but not limited to:
        i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for prescribers, actions taken to address non-compliance for each case, and which events lead to suspension or decertification from the REMS.
    b. Number and percent 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

4. REMS Website (per reporting period and cumulatively)
    a. Number of visits and unique visits to the REMS website
    b. Number of REMS materials downloaded or printed for each material

5. Coordinating Center Report (per reporting period)
    a. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.)
    b. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type
    c. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
    d. A summary report of corrective actions resulting from issues identified

B. Safe Use Behaviors

6. Safe Use Behaviors (per reporting period and cumulatively)
    a. Number of new patients treated with Soliris receiving meningococcal vaccination according to current ACIP recommendations for persons who have complement deficiency. Information regarding the vaccines administered is to include vaccine serotype, dosing, and timing of the vaccinations

C. Health Outcomes and/or Surrogates of Health Outcomes

7. Summary of cases of U.S. meningococcal infections in patients receiving Soliris (per reporting period and cumulatively)
    a. Summarize cases for the following timeframes:
        i. 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, to include the specific vaccines; the dates they were administered; your conclusions as to whether the vaccinations complied with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred

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; specifically report whether the patient:

1) was admitted to an intensive care unit

2) experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure

viii. causative meningococcal serogroup

ix. whether the Patient Safety Information card was presented during the process of the patient seeking treatment

8. Meningococcal Infections Rate (per reporting period and cumulatively)

   Rate (# cases/100,000 patient-years) of meningococcal infections; 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.

D. Knowledge (per reporting period)

9. 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).

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) 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 LABELING 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.

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 Meredith Hillig, M.S., Acting Safety Regulatory Project Manager, at 301-796-1218.

Sincerely,

{See appended electronic signature page}

Rosanna Setse, M.D., Ph.D.
Acting Deputy Director for Safety
Division of Non-Malignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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/

ROSANNA W SETSE
04/07/2020 12:00:00 AM