DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125166/368 & 125166/380

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Alexion Pharmaceuticals, Inc.
Attention: Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

Dear Ms. Lyons:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 30, 2013, and received September 30, 2013, submitted under section 351(a) of the Public Health Service Act for Soliris® (eculizumab).

We acknowledge receipt of your amendments dated December 5, 2013; January 17, 27, 31, February 5, 6, 19, 27, March 5, 20, April 4, 14, 16, and 18, 2014 and your risk evaluation and mitigation strategy (REMS) assessment dated November 15, 2013 and March 4, 2014.

This Prior Approval supplemental biologics application for Soliris® (eculizumab) provides supporting data to convert the accelerated approval to regular approval for the treatment of patients with atypical Hemolytic Uremic Syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy, which includes data from clinical trials conducted per two post marketing requirements PMR-172/1 and PMR-172/2.

APPROVAL & LABELING

We have completed our review of this supplemental 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 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 package insert 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 includes 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.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your April 16, 2014 submission containing final printed carton and container labels.

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated September 30, 2014 containing the final reports for the following postmarketing requirements listed in the September 23, 2011 approval letter for BLA 125166/172.

1. PMR 172/1: An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome. This trial will be amended to include pharmacokinetic, efficacy, and safety data from a minimum of five patients who are treated with eculizumab in each of the following age cohorts:

- 1 month to <24 months
- 2 to <5 years
- 5 to 12 years

Protocol:	November 2011
Trial Completion:	December 2013
Final Report	September 2014.

2. PMR 172/2: An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome. This trial will enroll a minimum of 30 patients.

Final Protocol submission:	June 2011
Trial Completion Date;	December 2012
Final Report Submission Date:	September 2013.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there is a post-marketing requirement listed in the September 23, 2011 approval letter and post-marketing commitments listed in the May 11, 2012 approval letter that are still open.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Soliris® (eculizumab) was originally approved on June 4, 2010, and a REMS modification was approved on September 21, 2011. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a change in the timetable for submission of assessments from annually to every two years with the next report to be submitted by June 1, 2015, and a revised REMS assessment plan.

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® (eculizumab) who are not enrolled
    c. Reasons that prescribers did not enroll
    d. Actions taken to ensure that all prescribers are enrolled

2. Patient enrollment
    a. The number of new patients treated with Soliris® (eculizumab) for the reporting period and cumulatively
    b. Demographics of patients treated with Soliris® (eculizumab) (gender, pediatric age group, diagnosis) for the reporting period and cumulatively
    c. Number of new patients treated with Soliris® (eculizumab) receiving meningococcal vaccination according to current recommendations for persons who have complement

deficiency for the reporting period and cumulatively

3. Summary of cases of invasive meningococcal infections (US) provided in the most recent PSUR submitted to the Soliris® (eculizumab) BLA, with a link to that PSUR

4. Rate (number of cases per 100,000 Soliris® (eculizumab) patients) of invasive meningococcal infections for the reporting period and cumulatively; rates for U.S. cases, worldwide cases, and relevant age subgroups (pediatric cases, elderly cases) may also be calculated and provided

5. An assessment of prescriber and patient understanding regarding the safe use of Soliris® (eculizumab) (i.e., the results of surveys administered to prescribers and patients).

6. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24 including failures to adhere to distribution and dispensing requirements and corrective actions taken to address noncompliance

7. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

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.

Your proposed modified REMS, submitted on April 17, 2014, and appended to this letter, is approved.

In addition to the assessments submitted according to the timetable included in the approved REMS, 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.

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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the 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

NEW SUPPLEMENT FOR BLA 125166
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125166 REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

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(s) 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(s), 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 or by fax to 301-847-8444.

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 Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

EDVARDAS KAMINSKAS
04/30/2014