BLA 761108/S-005

SUPPLEMENT APPROVAL

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

Dear Ms. Lyons:

Please refer to your supplemental biologics license application (sBLA), dated and received December 11, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ultomiris (ravulizumab-cwvz) injection.

This Prior Approval supplemental biologics application provides for a new concentration, 100 mg/mL, with two vial presentations: 300 mg/3 mL and 1100 mg/11 mL, for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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.

MANUFACTURING LOCATIONS

You are approved to manufacture ravulizumab 100 mg/mL formulated drug substance (b) (4)

The 100 mg/mL final formulated drug product will be manufactured at Alexion Athlone Manufacturing Facility, Athlone, Ireland.

DATING PERIOD

The dating period for Ultomiris 100 mg/mL shall be 18 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) °C.

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 FDA.gov,[1] 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, submitted on August 21, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761108/S-005**." 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 (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3947-1 Conduct a low endotoxin recovery (LER) study at process relevant temperature [redacted] (b) (4) and duration [redacted] (b) (4) to ensure the kinetic turbidimetric test method can reliably detect bacterial endotoxin in 100 mg/mL drug product. If the LER study shows endotoxin recovery below 50% at process relevant conditions, develop an alternate endotoxin test method which mitigates LER.

The timetable you submitted on October 5, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2021

3947-2 Provide endotoxin method qualification results from three batches for the [redacted] (b) (4)

The timetable you submitted on October 5, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2021

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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 Charlene Wheeler, Acting Chief, Project Management Staff, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Non-Malignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
  - 300 mg/3 mL container labeling
  - 300 mg/3 mL carton labeling
  - 1100 mg/11 mL container labeling
  - 1100 mg/11 mL carton labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

---

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/

ANN T FARRELL
10/09/2020 10:42:25 AM