NDA 216718/S-008
NDA 216718/S-009

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS

Biogen U.S. Corporation
Attention: Priya Singhal, MD, MPH
Executive Vice President, Head of Development
225 Binney Street
Cambridge, MA 02142

Dear Dr. Singhal:

Please refer to your supplemental new drug applications (sNDAs) dated and received June 20, 2024, and your amendment(s), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Skyclarys (omaveloxolone) capsules.

Prior Approval sNDA S-008 provides for changes in the following section of the Prescribing Information (PI):

Section Number and Title	Description of Change
12.2 Pharmacodynamics	Revisions under the Cardiac Electrophysiology heading to note that clinically significant QTc prolongation was not observed in healthy subjects with administration of supratherapeutic doses, based on the results from the completed study for PMR 4410-7.

Prior Approval sNDA S-009 provides for changes in the following sections of the PI:

Section Number and Title	Description of Change
2.2 Recommended Dosage	Addition of “or 2 hours after eating” to further describe empty stomach administration
6.2 Postmarketing Experience	Addition of hypersensitivity (urticaria, rash)
7.1 Effect of Other Drugs on SKYCLARYS	Revision from “may” to “is expected to result in clinically significant” with respect to CYP3A4 Inducers decreasing the exposure of omaveloxolone, based on the results from the completed study for PMR 4410-8.
8.1 Pregnancy	Addition of the pregnancy exposure registry contact information.

12.3 Pharmacokinetics	• Revisions under the Specific Populations heading regarding information from a completed population pK analysis of patients with mild renal impairment. • Revisions under the Drug Interactions heading regarding CYP3A Inducers based on the completed study for PMR 4410-8, which confirmed the decreased exposure of omaveloxolone with concomitant administration. • Revisions under the Drug Interactions heading regarding completed in-vitro studies that showed omaveloxolone is an inducer of CYP3A4 and CYP2C19, but is not an inducer of CYP2C8 and CYP2C9.
13.1 Nonclinical Toxicology	Revisions under the Carcinogenesis heading regarding the completed 26-week carcinogenicity study in mice that showed no increase in tumors. This labeling change was in response to the Agency's request noted in the March 14, 2024, PMR Fulfillment letter for PMR 4410-3.
17 Patient Counseling Information	Revisions under the Pregnancy and Administration headings pertaining to the edits in sections 8.1 and 2.2, respectively.
Patient Information	Revisions pertaining to the edits in sections 8.1 and 2.2 of the PI.

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] 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).

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 are required to contain an assessment of the safety and effectiveness of the product for the claimed indication 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 REQUIREMENT

We have received your submissions dated April 24, 2024, and March 12, 2024, containing the final reports for the following postmarketing requirements listed in the February 28, 2023, approval letter.

---

[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.

4410-7 Conduct a clinical trial to assess the risk of QT prolongation with omaveloxolone to exclude mean QTc effects greater than 10 ms.

4410-8 Conduct a clinical drug interaction study to determine the effect of concomitant administration of a moderate CYP3A4 inducer on pharmacokinetics of omaveloxolone in healthy volunteers. Design and conduct the trial in accordance with the 2020 FDA guidance for industry *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions*. (https://www.fda.gov/media/134581/download)

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

We remind you that there are postmarketing requirements listed in the February 28, 2023, approval letter that are still open.

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that you provide a narrative summary including analysis of anaphylaxis and other serious hypersensitivity reactions as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval date.

Your analysis should include interval and cumulative data relative to the date of approval of Skyclarys. Your analysis should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

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]

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

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Brenda Reggettz, PharmD, Regulatory Health Project Manager, by email at Brenda.Reggettz@fda.hhs.gov or by phone at (240) 402-6220.

Sincerely,

{See appended electronic signature page}

Emily Freilich, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[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/

EMILY R FREILICH
12/20/2024 12:59:17 PM