NDA 203479/S-26

SUPPLEMENT APPROVAL

Douglas Pharmaceuticals America Limited
c/o PTS Consulting, LLC
Attention: Paul T. Sudhakar
President
6739 Valhalla Ct
Shawnee, KS 66217

Dear Paul Sudhakar:

Please refer to your supplemental new drug application (sNDA) dated and received March 26, 2025, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Versacloz (clozapine) oral suspension.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved clozapine Risk Evaluation and Mitigation Strategy (REMS), corresponding changes to the Boxed Warning, Warning and Precautions of the prescribing information, and the addition of a Medication Guide. This supplement is in response to our February 24, 2025, REMS Modification/Safety Labeling Change Notification letter.

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 shared system (SS) REMS for clozapine, of which Versacloz is a member, was originally approved on September 15, 2015, and the most recent REMS modification was approved on September 29, 2023. The SS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Because we determined that a REMS is no longer necessary to ensure the benefits of clozapine outweigh its risks, and to minimize the burden on the healthcare delivery system of complying with the REMS, you were required to submit a REMS modification to eliminate the REMS as outlined in our REMS Modification/Safety Labeling Change Notification letter dated February 24, 2025.

Elements to Assure Safe Use: We have determined that elements to assure safe use are no longer necessary based on the following data:

- Knowledge of the risk of severe neutropenia and the need for absolute neutrophil count (ANC) monitoring appears to be more broadly understood by prescribers, and information and training on clozapine and its safe use is more widely incorporated into medical training and healthcare systems today as compared to 1989 when clozapine was first approved. The knowledge gap has narrowed and guidelines and resources available to prescribers about clozapine have greatly expanded since the approval of clozapine.

- Even though the REMS has not been fully implemented due to administrative difficulties and FDA exercised enforcement discretion, the studies commissioned by FDA reveal evidence of ANC monitoring among patients using clozapine. The average frequency of testing is less than what is recommended in the labeling for the first 6 months; after the first 6 months, adherence is more consistent with labeling as monitoring frequency is reduced. Even with the absence of strict adherence to monitoring in the first 6 months, the incidence of severe neutropenia and clozapine-related mortality in these studies was substantially lower than before monitoring was recommended. Thus, we have been unable to determine the impact or benefit the REMS has had on mitigating the risk of severe neutropenia beyond what labeling alone could accomplish.

- There are unintended consequences of the Clozapine REMS that create undue burden on patient access.

- We also considered the advice of the November 19, 2024, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee. In general, the committee members agreed with the continued need to monitor ANCs; however, they concluded that the documentation of the ANC through the REMS and training for health care providers through the REMS are no longer necessary to ensure safe use of clozapine.

Implementation System: Because the elements to assure safe use requiring that pharmacies that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions are no longer necessary, the implementation system is also no longer necessary as an element of the REMS.

Because the elements to assure safe use and implementation system are no longer necessary to ensure the benefits of the drug outweigh the risks and to minimize the burden on the healthcare delivery system of complying with the REMS, a REMS is no longer required for clozapine.

SAFETY LABELING CHANGES

We also refer to our letter dated February 24, 2025, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for Versacloz. This information pertains to the risk of risk of severe neutropenia, as well as other risks associated with clozapine. Further, FDA is requiring a Medication Guide as part of approved clozapine labeling pursuant to 21 CFR 208.1.

This supplemental new drug application provides for revisions to the labeling for Versacloz to include the new safety information in the labeling, including a new Medication Guide.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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, Instructions for Use, and Medication Guide), 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]

[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.

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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).

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

CARTON AND CONTAINER LABELING

We acknowledge your May 13, 2025, submission containing final printed carton and container labeling.

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.

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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]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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).

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

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 Ermias Zerislassie, Associate Director for Postmarket Regulatory Science, at ermias.zerislassie@fda.hhs.gov or 301-796-2770.

Sincerely,

{See appended electronic signature page}

Bernard A. Fischer, M.D.
Deputy Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

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/

BERNARD A FISCHER
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