

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203479Orig1s000

Trade Name: Versacloz oral suspension 50 mg/mL.

Generic Name: clozapine

Sponsor: Douglas Pharmaceuticals America Ltd

Approval Date: February 6, 2013

Indications: For treatment resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder.

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 203479

NDA APPROVAL

Douglas Pharmaceuticals America Ltd
Attention: John Franolic, PhD
Vice President of Regulatory Affairs
VersaPharm Incorporated
1775 West Oak Parkway, Suite 800
Marietta, GA 30062

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) dated December 28, 2011, received January 6, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Versacloz (clozapine) oral suspension 50 mg/mL.

We acknowledge receipt of your amendments dated February 14, 2012, February 27, 2012, March 13, 2012, March 23, 2012, March 27, 2012, March 30, 2012, April 10, 2012, May 4, 2012, May 24, 2012, June 11, 2012, July 16, 2012, July 18, 2012, July 20, 2012, August 1, 2012, August 22, 2012, August 28, 2012, September 12, 2012, September 27, 2012, September 28, 2012, October 16, 2012, October 17, 2012, October 18, 2012, October 19, 2012, November 2, 2012, November 6, 2012, December 19, 2012, January 30, 2013, February 5, 2013, and February 6, 2013.

This new drug application provides for the use of Versacloz (clozapine) oral suspension for treatment resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder.

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 text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and patient package insert). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

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 January 30, 2013, submission containing final printed carton and container labels.

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.

We are waiving the pediatric study requirement for Versacloz for all ages (0-17) because the condition of treatment resistant schizophrenia is not applicable to the pediatric population in sufficient numbers to study.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 2012-1 An actual use human factors study of Versacloz (clozapine) in the United States in patients with schizophrenia. The study should include patients who are new to clozapine and patients who are stabilized on clozapine. The study should assess patients' ability to correctly measure doses of Versacloz (clozapine) using the approved Instructions for Use and packaging components.

The timetable you submitted on January 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 30, 2013
Study Completion:	August 30, 2013
Final Report Submission:	October 31, 2013

Submit clinical protocols to your IND 108466 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, the number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Versacloz (clozapine) oral suspension to ensure the benefits of the drug outweigh the risk of agranulocytosis.

Pursuant to 505-1(f)(1), we have also determined that Versacloz (clozapine) oral suspension can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of agranulocytosis that are listed in the labeling. The elements to assure safe use will help to assure appropriate patient selection for treatment with Versacloz (clozapine) and appropriate monitoring for development of agranulocytosis with Versacloz (clozapine) treatment.



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 REMS, received on January 6, 2012, amended on September 27, 2012, October 19, 2012, November 6, 2012, February 5, 2013, and February 6, 2013, and appended to this letter, is approved. The REMS consists of elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Versacloz (clozapine) oral suspension into interstate commerce.

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

1. Assessment of enrollment and discontinuation statistics for prescribers, pharmacies, and patients:
 - a. The number of patients enrolled in the Versacloz REMS (during the reporting period and cumulative).
 - b. The number of person-years for enrolled patients.
 - c. The number of patients who received Versacloz that were not enrolled (during the reporting period and cumulative).
 - d. The number of patients who stopped receiving Versacloz (during the reporting period and cumulative).
 - e. The number of prescribers enrolled in Versacloz REMS (during the reporting period and cumulative).
 - f. The number of pharmacies enrolled in Versacloz REMS (during the reporting period and cumulative).
2. Assessment of Versacloz Patient Registry Healthcare Providers Enrollment Forms, Pharmacy/Pharmacist Enrollment Forms, and Patient Registration Forms:
 - a. Number of incomplete enrollment forms and summary of most frequent missing information
3. Summary of annual accuracy audit from Versacloz Registry Protocol including a narrative summary of any corrective action taken
4. Assessment of prescribing and dispensing of Versacloz for ineligible patients, including a narrative summary of corrective action taken.
5. Assessment of nonenrolled prescribers and pharmacists who prescribe or dispense Versacloz, including a narrative summary of corrective action taken.
6. Assessment of prescriber and pharmacy compliance including:
 - a. Compliance with submission of WBC count and ANC within the appropriate timeframe depending on patient monitoring frequency (7, 14, 28-days) by assessing WBC count/ANC alerts and whether appropriate follow-up action was taken and by assessing lab value late list reports and whether appropriate follow-up action was taken
 - b. Compliance with submission of patient information to the Versacloz REMS after discontinuation of clozapine due to agranulocytosis
 - c. Compliance with changes in the frequency of monitoring as recommended dependent upon changes in a patients WBC count and ANC values.

7. Number of communications with Clozapine National Non-Rechallenge Masterfile (NNRM) including narrative reports of any patient who received Versacloz while listed on the NNRM.
8. Summaries of MedWatch forms submitted to FDA.
9. An assessment of wholesaler's compliance with limiting distribution of Versacloz to registered pharmacies.
10. Summaries of Versacloz quarterly safety meetings including issues discussed at the meeting and actions taken as a result.

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 assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS 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:

**NDA 203479 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 203479 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 203479
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 203479
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 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 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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>.

REPORTING REQUIREMENTS

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

- Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following :
 - All reports of errors that led to an overdose or underdose of the drug including any adverse events resulting from the overdose or underdose
- Submit as expedited reports within 15 days of receipt for the following:
 - All reports of product complaints related to the use of the oral syringes or product packaging

- Include a summary evaluation of each of these reports requested in the submission of the periodic reports for each reporting period; in addition to a summary of these events in the context of all overdose and underdose events reported for Versacloz.

If you have any questions, contact Sharonjit Sagoo, Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

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/

MITCHELL V Mathis
02/06/2013