DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019758/S-90

SUPPLEMENT APPROVAL

Heritage Life Sciences (Barbados), Inc.
Attention: Shontelle Murrell-Hinkson
Assistant Secretary
The Beach House
Holetown, St. James, Barbados

Dear Ms. Murell-Hinkson:

Please refer to your Supplemental New Drug Application (sNDA) received July 24, 2018 and amended on December 13, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 19758 Clozaril (clozapine HCl) 25 mg and 100 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Clozapine Risk Evaluation and Mitigation Strategy (REMS).

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 single, shared system Clozapine REMS, of which Clozaril is a member, was originally approved on September 15, 2015. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of the addition of educational materials, changes to the inpatient prescriber certification requirements and patient monitoring, and initiation of the operational restrictions for prescriber and pharmacy certification.

Your proposed modified REMS, submitted on July 24, 2018, amended and appended to this letter, is approved.

The timetable for submission of assessments must be revised. The timetable for submission of assessments of the currently approved program is at 6-months, and 12-months from the date of initial approval of the REMS (September 15, 2015), and then annually thereafter. With this modification the timetable for submission of assessments is: annually beginning February 28, 2020.

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

A. REMS Program Implementation and Operations

1. REMS Program Utilization:

   a. Pharmacies, Prescribers, Prescriber Designees, and Distributors:

      i. Number of each stakeholder, status of certification or enrollment (as applicable), and method of certification or enrollment (as applicable)

      ii. Summary of reasons certification or enrollment is incomplete for each stakeholder (Examples may include "Pharmacy unable to configure pharmacy management system," "Prescriber missing information on form," etc.)

   b. Patient Treatment Status by Patient Type (general population, BEN patients, NNRMF patients, hospice patients) for the reporting period and cumulatively:

      i. Active

      ii. Interrupted

      iii. Discontinued

   c. A nationally estimated number of patients that received a dispensed prescription for clozapine (all dosage forms) from U.S. outpatient retail pharmacies for the reporting period. Provide rationale for discrepancies between this estimate and the number of unique patients enrolled in the clozapine REMS and receiving at least one PDA during the reporting period.

2. Contact Center Report:

   a. Number of contacts

   b. Summary of reason for contacts (examples may include "Enrollment question," "Lab query," etc.) by reporter (i.e., pharmacy, prescriber, patient)

   c. Narrative of any corrective actions resulting from issues identified

3. Clozapine REMS Program Compliance (to be included in the REMS Assessment Report after full implementation):

   a. Audits

i. Summary of audit findings for audits conducted during the reporting period

ii. Summary of corrective actions taken to address findings, the status of the corrective actions, and any resulting preventative actions that were taken

b. Number of clozapine prescriptions dispensed that were written by non-certified prescribers (reported or detected through audit):

i. Actions taken (examples may include "Provision of clozapine program materials," "Prescriber becomes certified," etc.)

ii. Outcome of actions taken

c. Number of prescriptions dispensed by noncertified outpatient pharmacies and actions taken to prevent future occurrences (reported or detected through audit)

d. Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences

e. Number of times a clozapine prescription dispensed because a pharmacy bypassed REMS edits; and, if any such events occurred, describe how these events were identified, the root cause of the failure, and any corrective actions taken (reported or detected through audit). Stratify by pharmacy type (switch or non-switch)

f. Number of times a clozapine prescription was dispensed by a pharmacy for more than a 3-day supply during the 3-day/72-hour *Dispense Rationale* window

g. Number of patients receiving a clozapine prescription under a *Dispense Rationale* stratified by the number of prescriptions authorized under a *Dispense Rationale* per patient in a 6-month time-frame

i. Summary of outreach to prescribers and number of resulting prescriber certifications.

h. Number of prescriptions dispensed under a *Dispense Rationale* stratified by prescriber

i. Number of PDA without current lab value based on the patient's monitoring frequency (7/15/31), provided as

(a) Total number of individual patients receiving PDA without current lab (i.e., aggregate)

(b) Number of PDAs for each unique patient without current lab; provide range and average number of PDAs per patient

j. Noncompliance with the Clozapine REMS Program requirements, source of report, and any corrective action or resolution

i. Number of PDAs without ANC (excluding hospice patients) and number of these resulting in clozapine dispensing

ii. Number of PDAs without a *Treatment Rationale* provided when the ANC was unacceptable, and number of these resulting in clozapine dispensing

4. Barriers or Delays in Patient Access: Provide outcome wherever possible

a. False negatives: e.g., all entities are certified, but system generated a prescription rejection notice

b. Inadvertent enrollment deactivations or failures to notify enrollees of forthcoming enrollment expirations

c. Reported lack of certified prescribers and/or pharmacies in a patient's local area

d. Unintended system interruptions and resolutions

e. For PDAs via electronic verification: Number of times and reasons a manual back-up system was used to validate a prescription and source of problem (e.g., switch level, pharmacy level, REMS database, etc.)

5. Inappropriate Patient Access:

    a. Inpatient pharmacy dispensing for outpatient use (reported or detected through audit)

    b. False positives: e.g., one or all entities were not certified but system verified dispensing/generated a PDA

6. Evaluation of Safe-Use Behaviors:

    a. Prescription Rejections:

        i. Number of unique prescriptions submitted for authorization

        ii. Number of unique prescriptions submitted for authorization that did not encounter any REMS-related rejections prior to being authorized stratified by authorization type (Clozapine REMS Program Website PDA or pharmacy claims PDA)

        iii. Number of unique prescriptions submitted for authorization that encountered any REMS-related rejections, stratified by authorization type (Clozapine REMS Program Website PDA or pharmacy claims PDA)

        iv. Mean, median, and range or the duration of time to authorize stratified by authorization type

        v. Provide reasons for prescription rejections stratified by type of PDA (via pharmacy management system or Clozapine REMS Program Website) and duration of time to authorize prescription if initially rejected

    b. Treatment Rationales:

        i. Number of Treatment Rationales submitted, stratified by type

        ii. Mean number of Treatment Rationales submitted per prescriber

    c. Number of notifications and alerts sent, stratified by type and stakeholder type (prescriber, pharmacy) and resulting actions by stakeholder (clozapine discontinued, pharmacy became enrolled, etc.)

(a) For overdue lab notifications and severe neutropenia notifications, provide the number of notifications per unique patient and any actions by stakeholder (clozapine discontinued, pharmacy became enrolled, etc.) resulting from the notification.

7. Evaluation of Knowledge/Surveys:

   a. An evaluation of knowledge of certified prescribers of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

   b. An evaluation of knowledge of authorized representatives and pharmacists of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

   c. An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and the need for appropriate monitoring

8. Evaluation of Required Monitoring:

   d. Total instances of severe neutropenia for unique patients (reported as lowest ANC for each unique patient whose ANC drops below 500/μL within each month)

   e. Total instances of neutropenia for unique patients (reported as lowest ANC for each unique patient whose ANC drops below 1500/μL, but remains at 500/μL or above within each month)

9. Clozapine REMS Program Outreach and Communication after the REMS modification in 01/2019 and after any subsequent modifications that are approved in each assessment period:

   a. Dates of distribution of the *Dear HCP Letter, Dear Distributor Letter, Dear Professional Society Letter, Chain Pharmacy Letter, Inpatient Pharmacy Letter, Outpatient Pharmacy Letter (Non-switch), Outpatient Letter (Switch),* and *Prescriber Letter* and the numbers sent on each date. Provide a list of the documents included with each distribution including the revision date

   b. Number of undeliverable and returned communications for each distribution date, by method of distribution

   c. A summary of the Clozapine REMS Program Website utilization

10. Knowledge Assessments:

a. Number of completed *Clozapine REMS Knowledge Assessment for Healthcare Providers* (KAs) for certified prescribers and pharmacy authorized representatives, and pharmacy staff that have elected to take the KA, including method of enrollment and number of attempts to complete, by stakeholder

b. Summary of the most frequently missed KA questions, stratified by prescriber and pharmacy

c. A summary of potential comprehension or perception issues identified with the KA

d. Proposed remediation for *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and/or the *Clozapine REMS Knowledge Assessment for Healthcare Providers*

11. The Important Program Update on the Clozapine REMS Program Website is used to communicate important program changes to stakeholders. This section on the website will provide frequent updates to stakeholders regarding the program. A summary of the number of updates communicated in this section of the website will be provided during the assessment reporting period.

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 1 or more such goals or such elements should be modified

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that 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. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

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 19758 REMS 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.

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.

Prominently identify any 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:

NDA 19758 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 19758/S-
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 19758/S-
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 19758/S-
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 19758/S-
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 19758

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

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, call Ermias Zerislassie, Safety Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Division Director Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
REMS

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/

TIFFANY R FARCHIONE
01/16/2019 12:15:13 PM
On behalf of Mitch Mathis