DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021590/S-014/S-027

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals, Inc.
Attention: Mike Johnston
Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Mr. Johnston:

Please refer to your Supplemental New Drug Applications (sNDAs) dated October 3, 2008 (S-014), and September 3, 2015 (S-027), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fazaclo (clozapine) Orally Disintegrating Tablets, 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg.

We also acknowledge receipt of your amendments to Supplement 014 dated October 29, 2008, March 23, 2011, July 27, 2012 dated, August 13, 2012, September 27, 2012, September 26, 2014, January 9, 2015, April 24, 2015, July 17, 2015, September 4, 2015, and September 14, 2015.

The "Prior Approval" supplemental new drug application, S-027 provides for changes to the Contraindications, Boxed Warning, Warnings and Precautions, Dosage and Administration, and Use in Specific Populations sections of the labeling to update the neutropenia monitoring algorithms and associated Fazaclo (clozapine) treatment recommendations; and to accommodate for Fazaclo (clozapine) treatment for patients with benign ethnic neutropenia.

The "Prior Approval" supplemental new drug application S-014 provides for a proposed risk evaluation and mitigation strategy (REMS) for Fazaclo (clozapine) and was submitted in accordance with section 909(b)(3) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified Fazaclo (clozapine) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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, text for the patient package insert, 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 titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Under section 909(b)(1) of FDAAA, we identified Fazaclo as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520. Under section 909(b)(3), you were required to submit a proposed REMS for Fazaclo.

Your proposed REMS, submitted October 03, 2008, last amended on September 14, 2015 and appended to this letter, is approved. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

The REMS will use a shared system for the ETASU, the implementation system, and the REMS assessments. This shared system, known as the Clozapine REMS Program, includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

The approval of the REMS is concurrent with the approval of new labeling language, which is not supported by the existing six individual registries (the "legacy risk management systems"). To support continued treatment of patients during the Clozapine REMS Program 90-day transition period, this REMS includes the following requirements:

1. For 30 calendar days after the date of this letter,
    a. Prescribers and pharmacies must continue to use the legacy risk management systems for certification, patient enrollment, and monitoring, including reporting of ANC values.
    b. All legacy risk management system requirements remain in effect.
2. Beginning 30 calendar days after the date of this letter,
    a. All clozapine patient registry websites under the legacy risk management systems must automatically redirect to the Clozapine REMS Program website.
    b. All phone and fax numbers previously associated with individual clozapine patient registries under the legacy risk management systems must automatically transfer to the Clozapine REMS Program.
    c. The Clozapine REMS Program must be fully functional, with the following exceptions:
        i. Electronic telecommunication verification that allows a pharmacy or group of pharmacies to receive electronic authorization to dispense through a pharmacy network or pharmacy switch will not be available.
        ii. Pre-Dispense Authorizations will not be available.
        iii. Wholesalers and distributors must distribute only to pharmacies either enrolled in a registry under a legacy risk management system or certified in the Clozapine REMS program.
        iv. Prescribers who are certified under a legacy clozapine risk management program may continue to prescribe clozapine without immediately becoming certified in the Clozapine REMS Program, but may only provide prescriptions to their existing patients who are continuing uninterrupted treatment begun under one of the legacy risk management systems. Prescribers must enroll in the Clozapine REMS Program to prescribe for any other patients.
3. Beginning 72 calendar days after the date of this letter, all prescribers must be certified in the Clozapine REMS program to prescribe clozapine for any patient.
4. Beginning 90 calendar days after the date of this letter, all elements of the Clozapine REMS Program must be fully implemented and functional in accordance with the approved REMS.

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

A. Background REMS Program Implementation and Operations
   1. REMS Program Utilization

      a) Pharmacies, Prescribers, Prescriber Designees and Distributors
         (1) Number of each stakeholder, status of certification or enrollment (as applicable), and method of certification or enrollment (as applicable)

         (2) 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 Status by Patient Type (General population, BEN patients, NNRMF patients, hospice patients)
         (1) Active
         (2) Interrupted
         (3) Discontinued

   2. Contact Center Report
      a) Number of Contacts
      b) Summary of reason for call (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 beginning with the 12 Month REMS Assessment Report)
      a) Audits
         (1) Summary of audit findings for audits conducted during the reporting period.
         (2) 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)
         (1) Actions taken (Examples may include "Provision of clozapine program materials", "Prescriber becomes certified", etc.)
         (2) 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 audits 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 vs non-switch)

f) Noncompliance with the Clozapine REMS Program requirements, source of report, and any corrective action or resolution
   (1) Number of PDAs without ANC (excluding hospice patients) and number of these resulting in clozapine dispensing
   (2) Number of PDAs without treatment rationales provided when ANC unacceptable, and number of these resulting in clozapine dispensing

4. Barriers or Delays in Patient Access
   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

B. Evaluation of Safe Use Behaviors
   1. Prescription Rejections
      a) Number of pre-dispense authorizations (PDAs) that did not encounter any REMS- related rejections prior to being authorized
      b) Total number of authorizations that encountered any REMS-related rejections
      c) Mean, median, and range of the duration of time to authorize
      d) Provide reasons for prescription rejections stratified by type of PDA (via pharmacy management system or clozapine REMS) and duration of time to authorize prescription if initially rejected

   2. Treatment Rationales
      a) Number of treatment rationales submitted, stratified by type
      b) Mean number of treatment rationales submitted per prescriber

   3. Number of notifications and alerts sent, stratified by type and stakeholder type (Prescriber, Pharmacy)

C. Evaluation of Knowledge/Survey

1. An evaluation of knowledge of certified prescribers of the risk of severe neutropenia, appropriate monitoring of clozapine, and the REMS requirements
2. An evaluation of knowledge of authorized representatives and pharmacists of the risk of severe neutropenia, appropriate monitoring of clozapine, and REMS requirements
3. An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and appropriate monitoring of clozapine

D. Evaluation of Required Monitoring

1. 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)
2. Total instances of neutropenia for unique patients (reported as lowest ANC for each unique patient whose ANC drops below 1500/µL within each month)

E. With respect to each goal included in the REMS, an assessment of the extent to which the approved REMS, including each element of the REMS, is meeting the goal or whether one or more such goals or such elements should be modified.

F. The Clozapine REMS Program Transition Status (to be included in the 6 Month REMS Assessment Report only)

1. Date when REMS materials became available to healthcare professionals on the website and via the contact center
2. Dates healthcare professionals could become certified online, by mail, and by fax
3. Automatic data transition:
   a) Total number of prescribers automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value within the past 3 years), and date the transition was completed
   b) Total number of prescriber designees automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value within the past 3 years), and date the transition was completed
   c) Number of pharmacies automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value in one or more of the individual clozapine patient registries within the past 3 years), and date the transition was completed
   d) Total number of patients transferred into the Clozapine REMS Registry (must have a valid ANC or WBC lab value in one or more of the individual clozapine patient registries within the past 3 years)
   e) Number of patients automatically transitioned into the Clozapine REMS Registry who previously were on the National Non-Rechallenge Master File

(NNRMF), and the number that have been flagged as such in the Registry

f) Dates individual clozapine patient registry websites began redirecting visitors to the Clozapine REMS Program

G. Clozapine REMS Program Outreach and Communication (to be included in the 6 and 12 Month REMS Assessment Report only)

1. Dates of distribution of the Dear HCP Letter, Dear Distributor Letter, Dear Professional Society Letter and the numbers sent on each date. Provide a list of the documents included with each distribution including the revision date.
2. Number of undeliverable and returned communications for each distribution date, by method of distribution
3. A summary of the Clozapine REMS Program website utilization

H. Knowledge Assessments (to be included in the 6 and 12 Month REMS Assessment Report only)

1. Number of completed Knowledge Assessment for Healthcare Providers (KAs) for certified prescriber and pharmacy authorized representative, and pharmacy staff that have elected to take the KA, including method of enrollment and number of attempts to complete, by stakeholder
2. Summary of the most frequently missed KA questions, stratified by prescriber and pharmacy
3. A summary of potential comprehension or perception issues identified with the KA
4. Proposed remediation for Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers and/or the Knowledge Assessment for Healthcare Providers

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 of 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). 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, proposed 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 the 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 rational 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 a REMS modification,* 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 submissions 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 021590 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.

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 the 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 021590 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021590/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021590/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021590/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021590/S-000
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 REVISION FOR NDA 021590

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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 the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

SPECIAL REPORTING FOR NEUTROPENIA ADVERSE EVENTS

In your email communication dated April 9, 2015, you agreed to the following special reporting for neutropenia adverse events:

1. Expedite cases of neutropenia with an ANC <1000/µL (i.e., submit these cases as 15-day Alert reports) that would not normally be required to be submitted because severe neutropenia is a labeled event. This special reporting applies to cases collected by the registry, as well as cases spontaneously reported to an individual sponsor.
2. Review, prepare, and submit the 15-day Alert reports as described under 21 CFR 314.80, which includes conducting follow-up (21 CFR 314.80(c)(1)(ii).
3. Have written procedures for identifying an adverse event report meeting the criteria (serious and non-serious outcomes for all cases of neutropenia with an ANC <1000/µL) and submitting the 15-day Alert report to FDA.

We also request that clozapine sponsors have a procedure for identifying a responsible sponsor when an adverse event report is received for a clozapine product and the sponsor is unknown. There must be a responsible sponsor identified to conduct follow-up and submit the report to FDA.

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 Ann Sohn, Regulatory Project Manager, at (301) 796-2232 or email at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
REMS
REMS Program Materials

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
09/15/2015