DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 203039

ANDA APPROVAL

Barr Laboratories, Inc.
425 Privet Road
Horsham, PA 19044
Attention: Rich Leone
Senior Director, Regulatory Affairs, U.S. Generics

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 8, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Clozapine Orally Disintegrating Tablets, 150 mg and 200 mg.

Reference is also made to the complete response letter issued by this office on June 17, 2014, and to your amendments dated July 28, and September 26, 2014; January 8, April 24, May 13, July 17, August 13, September 4, September 14, October 1, and October 21, 2015.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Division of Bioequivalence has determined your Clozapine Orally Disintegrating Tablets, 150 mg and 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Fazaclo Orally Disintegrating Tablets, 150 mg and 200 mg of Jazz Pharmaceuticals III International Ltd (Jazz). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Jazz's Fazaclo, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,024,981 (the '981 patent)	April 9, 2018
6,221,392 (the '392 patent)	April 9, 2018
6,106,861 (the '861 patent)	December 5, 2017

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Clozapine Orally Disintegrating Tablets,

150 mg and 200 mg, under this ANDA. You have notified the Agency that Barr Laboratories, Inc. (Barr) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement was brought against Barr within the statutory 45-day period.

With respect to 180-day generic drug exclusivity, we note that Barr was the first ANDA applicant for Clozapine Orally Disintegrating Tablets, 150 mg and 200 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Barr may be eligible for 180 days of generic drug exclusivity for Clozapine Orally Disintegrating Tablets, 150 mg and 200 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Barr failed to obtain tentative approval of this ANDA within 40[1] months after the date on which the ANFDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval within 30 months). The Agency is not, however, making a formal determination at this time of Barr's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Barr begins commercial marketing of Clozapine Orally Disintegrating Tablets, 150 mg and 200 mg, or (b) at any time prior to the expiration of the '981, '392, and '861 patents if Teva has not begun commercial marketing. Please submit correspondence to this ANDA informing the Agency of the date commercial marketing begins.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) 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(i) of FDCA, an ANDA is required to have a REMS if the applicable listed drug has an approved REMS.

[1] For applications submitted between January 9, 2010 and July 9, 2012, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-114) extended the 30-month period to 40 months.

The details of the REMS requirements were outlined in the REMS notification letter dated November 5, 2012. In that letter, you were also informed that pursuant to section 505-1(i) of the FDCA, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for the elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on September 14, 2015, and appended to this letter, is approved. The REMS consists of ETASU and an implementation system.

The REMS uses 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 transition period, this REMS includes the following requirements:

1. Until October 15, 2015:
    a. Prescribers and pharmacies must continue to use the legacy risk management systems for certification, patient enrollment, and monitoring, including reporting of Absolute Neutrophil Count (ANC) values.
    b. All legacy risk management system requirements remain in effect.
2. Beginning on October 15, 2015:
    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 on November 26, 2015, all prescribers must be certified in the Clozapine REMS program to prescribe clozapine for any patient.
4. Beginning on December 14, all elements of the Clozapine REMS Program must be fully implemented and functional in accordance with the approved REMS.

Under section 505-1(g)(2)(C) of the FDCA, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. Please submit an assessment to your application at the same time as the sponsors of the NDA products in the REMS. The details for what should be included in your joint REMS assessments completed under the Clozapine REMS are listed in Appendix 1.

We remind you that 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 section 505-1(f)(8) of the FDCA prohibits holders of an approved covered application from using any element to assure safe use 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:

ANDA 203039 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 203039/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 203039/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 203039/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

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 ANDA 203039

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.

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 the 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

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

PROMOTIONAL MATERIALS

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products.

Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

Sincerely yours,

Carol A. Holquist -S

Digitally signed by Carol A. Holquist -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052464, cn=Carol A. Holquist -S
Date: 2015.11.25 14:29:56 -05'00'

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
REMS