DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 090308

TENTATIVE APPROVAL/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 December 28, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Clozapine Orally Disintegrating Tablets, 12.5 mg, 25 mg and 100 mg.

Reference is also made to the complete response letter issued by this office on June 23, 2014, and to your amendments dated September 5, 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. However, we are unable to grant final approval to your Clozapine Orally Disintegrating Tablets, 12.5 mg, at this time because of the exclusivity issue noted below. Therefore, only your Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg, is **approved**. The 12.5 mg strength is **tentatively approved**.

The referenced listed drug (RLD) upon which you have based your ANDA, Fazaclo, Orally Disintegrating Tablets, 12.5 mg, 25 mg and 100 mg, of Jazz Pharmaceuticals III International Ltd (Jazz), 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 the '981, '392, and '861 patents[1] under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable,

[1] The agency notes that the '861 patent for the 25 mg and 100 mg strengths was listed in the Orange Book after submission of your ANDA. Litigation, if any, with respect to this patent would not create a statutory stay of approval.

or will not be infringed by your manufacture, use, or sale of Clozapine Orally Disintegrating Tablets, 12.5mg, 25 mg and 100 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 for the '861 patent within the statutory 45-day period. You have also notified the Agency that litigation was initiated against Barr for infringement of the '981 and '392 patents within the statutory 45-day period in the United States District Court for the District of Delaware [CIMA LABS, INC., AZUR PHARMA LIMITED, and AZUR PHARMA INTERNATIONAL III LIMITED v. BARR LABORATORIES and BARR PHARMACEUTICALS, INC., Civil Action No. 1:09-cv-00349-LPS (12.5 mg strength) and CIMA LABS, INC., AZUR PHARMA LIMITED, and AZUR PHARMA INTERNATIONAL III LIMITED v. BARR LABORATORIES, INC and BARR PHARMACEUTICALS, LLC., Civil Action No. 1:08-cv-00531-LPS (25 mg and 100 mg strengths)]. Additionally, you have notified the Agency that the cases were dismissed.

I. Approval of Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg

With respect to Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg, we 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, 25 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the RLD, Jazz's Fazaclo. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

With respect to 180-day generic drug exclusivity, we note that Barr was the first ANDA applicant for Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg, to submit a substantially complete ANDA with a paragraph IV certification. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, runs from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). In this instance, the 180-day exclusivity for these two products was triggered and ran under section 505(j)(5)(B)(iv)(I) of the FD&C Act commencing on August 30, 2012, with the marketing of an authorized generic product for Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg, by Teva Pharmaceuticals USA Inc.

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 FD&C Act 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 the FD&C Act, an ANDA is required to have a REMS if the applicable listed drug has an approved REMS.

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 FD&C Act, 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 elements to assure safe use, 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.

To support continued treatment of patients during the Clozapine REMS Program transition period, this REMS includes the following requirements:

1. Beginning on October 15, 2015:
    a. 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.

2. Beginning on November 26, 2015, all prescribers must be certified in the Clozapine REMS program to prescribe clozapine for any patient.
3. 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 FD&C Act, 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 FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act 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 090308 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 090308/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 090308/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 090308/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 090308

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.

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.

We remind you that you must comply with the requirements for the approved ANDA described in 21 CFR 314.80-81.

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.

II. Tentative Approval of Clozapine Orally Disintegrating Tablets, 12.5 mg

Your Clozapine Orally Disintegrating Tablets, 12.5 mg, is tentatively approved because of another applicant's 180-day generic drug exclusivity for this strength. Prior to the submission of your ANDA, another applicant submitted a substantially complete ANDA providing for Clozapine Orally Disintegrating Tablets, 12.5 mg, and containing a paragraph IV certification. Thus, your Clozapine Orally Disintegrating Tablets, 12.5 mg, will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

Our decision to tentatively approve your Clozapine Orally Disintegrating Tablets, 12.5 mg, is based upon information available to the Agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

To reactivate your ANDA prior to final approval of the 12.5 mg strength, please submit a "***MINOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED***" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively

approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a ***MINOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED***.

In addition to the amendment requested above, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA for the 12.5 mg strength, or may result in a delay in the issuance of the final approval letter for this additional strength.

Any significant changes in the conditions outlined in this ANDA for the 12.5 mg strength, as well as changes in the status of the manufacturing and testing facilities' cGMPs, are subject to Agency review before final approval of the ANDA for the 12.5 mg strength will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval of the 12.5 mg strength may also result in a delay in the issuance of the final approval letter for this strength.

Please note that under section 505 of the FD&C Act, your Clozapine Orally Disintegrating Tablets, 12.5 mg, may not be marketed without final Agency approval. The introduction or delivery for introduction into interstate commerce of your Clozapine Orally Disintegrating Tablets, 12.5 mg, before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter for this strength, your 12.5 mg strength will not be deemed to be approved for marketing under section 505 of the FD&C Act, and will not be listed in the "Orange Book."

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.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give

priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Scott Dallas, Regulatory Project Manager, at (240) 402-8618.

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 14:04:35 -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