DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 201824

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 28, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Clozapine Orally Disintegrating Tablets, 12.5 mg, 25 mg and 100 mg.

Reference is also made to your amendments dated October 7, 2010; August 9, August 11, August 30, November 29, 2011; January 4, May 9, August 6, August 29, November 8, 2012; January 22, February 12, March 22, August 13, 2013; September 26, 2014; January 8, April 24, May 14, July 17, September 3, and September 14, 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, are **approved**. The 12.5 mg strength is **tentatively approved**.

The RLD upon which you have based your ANDA, Fazaclo, Orally Disintegrating Tablets, 12.5 mg, 25 mg and 100 mg of Jazz Pharmaceuticals, Inc. (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 each of the patents under section 505(j)(2)(A)(vii)(IV) of FDCA stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Clozapine Orally Disintegrating Tablets, 12.5 mg, 25 mg and 100 mg, under this ANDA. You have notified the Agency that Mylan

Pharmaceuticals Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of FDCA, and that litigation was initiated against Mylan 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 MYLAN PHARMACEUTICALS, INC., Civil Action No. 1:10-cv-00625-UNA]. Additionally, you have notified the Agency that the case was dismissed.

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

With respect to Clozapine Orally Disintegrating Tablets, 25 mg and 100mg, 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 reference listed drug (RLD), Fazaclo of Jazz Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

Under section 506A of FDCA, 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.

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 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.

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 Absolute Neutrophil Count (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.

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 201824 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 201824/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 201824/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 201824/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 201824

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 FDCA, 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 to the '981, '392, and '861 patents. Thus, your Clozapine Orally Disintegrating Tablets, 12.5 mg, will be eligible for final approval on the date that is 180 days after the date the Agency receives notice, with respect to the other ANDA, of the commercial marketing date identified in section 505(j)(5)(B)(iv) of FDCA.

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 FDCA, 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 FDCA. Also, until the Agency issues the final approval letter for this strength, your 12.5mg mg strength will not be deemed to be approved for marketing under section 505 of FDCA, and will not be listed in the "Orange Book."

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.

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 John Ibrahim, Regulatory Project Manager, at (240) 402-5919.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.09.15 13:24:30 -04'00'

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

ENCLOSURES:
REMS
REMS Program Materials