

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75417

CORRESPONDENCE

ANDA 75-417

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

APR 22 1999

Dear Sir:

This is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clozapine Tablets, 25 mg and 100 mg.

Reference is also made to your amendment dated February 12, 1999.

We have reviewed your proposed Clozapine Patient Protection Program and have the following comments:

1. HEALTH CARE PROVIDER REGISTRATION (New Health Care Providers Registering with CPPP)

Your brief discussion of the independent quality assurance committee on page 98, second paragraph, of the CPPP summary does not adequately describe the composition, role, and functioning of this body. Please provide this information.

2. TRACKING PATIENTS: WEEKLY AND BI-WEEKLY WBC MONITORING (Physician Declares Patient "Interrupted Therapy")

The statement: "Any patient whose therapy has been interrupted must begin a new six month cycle of weekly WBC count monitoring" is true in the context of your definition of "interrupted therapy" on page 97, which requires that an abnormal blood event have occurred. However, using a broader definition, if the interruption in treatment was not related to a blood event, this would not be consistent with current labeling for clozapine products. Specifically, within the first six months of treatment, if there were no abnormal blood events and the treatment interruption was not longer than one month, the six month "clock" need not be reset. Also, after the first six months, if there were no abnormal blood events and the

interruption was not longer than one year, biweekly monitoring may continue. The flowcharts on pages 113 and 115 do make this distinction between "interrupted therapy" and "break", respectively. Please make this distinction in the CPPP summary for clarity.

3. Please describe your system for monitoring compliance with the CPPP and what action will be taken in instances of non-compliance.
4. Describe your plan for auditing the distribution of clozapine by wholesalers to pharmacies.
5. Include absolute neutrophil count (ANC) criteria along with the WBC count criteria (i.e., your monitoring system, flow diagrams, etc.)
6. Please add a block for the patient's middle initial on your registration and reporting forms.
7. To ensure that adequate space has been provided and that information will be printed more clearly and legibly, please provide individual blocks for the patient's initials, social security number, etc., on your multiple patient WBC count reporting form.
8. For traveling patients:
 - a. You state that if no registered pharmacy is accessible, the physician may register with a pharmacy to form a protection group. How would the pharmacist be briefed about clozapine?
 - b. Novartis indicates that they will express mail medication to patients unable to get it at the vacation site. Do you have similar plans?
9. For physicians and pharmacists new to clozapine, what methods/materials will Mylan use to orient them to the drug and CPPP?
10. A phone number does not appear on any of the forms you submitted for review. How can a member of the protection group reach you with concerns or questions, especially if Internet access is not available? Will staff be available for emergencies?

Please respond to the Agency's comments concerning your proposed Clozapine Patient Protection Program, and submit as correspondence for our review and comment. Please note that we reserve the right to request further changes if deemed necessary prior to approval of this application.

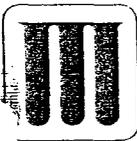
Sincerely yours,

ISI
for 4-22-1999
Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-417
Dup/Division File
HFD-610

Letter out

Endorsements:
HFD-613 *And Nelson 4/21/99*
HFD-613



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAY 20 1999

*NAI. Reviewed by J. Nelson
5/26/99*

NDA ORIG AMENDMENT

N/FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: CLOZAPINE TABLETS, 25MG AND 100MG
ANDA #75-417
RESPONSE TO AGENCY CORRESPONDENCE DATED APRIL 22, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the Agency's April 22, 1999, correspondence providing comments on Mylan's proposed Clozapine Patient Protection Program. For the convenience of the reviewer, a copy of the April 22, 1999, correspondence is provided in Attachment 1.

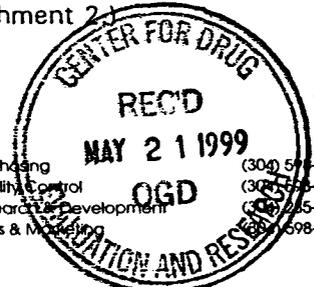
Mylan wishes to amend this application with a revised monitoring program to incorporate the Agency's April 22, 1999 comments and to include additional program changes that are described within this amendment. Mylan has changed the name of the program from Clozapine Patient Protection Program "CPPP" to Clozapine Prescription Access System "CPAS". A revised program summary is provided in Attachment 2, the revised flowcharts in Attachment 3 and the revised forms in Attachment 4. A detailed description of the changes made in the program in response to comments received from the Agency is provided below.

PROGRAM REVISIONS IN RESPONSE TO AGENCY COMMENTS

FDA COMMENT 1. HEALTH CARE PROVIDER REGISTRATION (New Health Care Providers Registering with CPPP)

Your brief discussion of the independent quality assurance committee on page 98, second paragraph, of the CPPP summary does not adequately describe the composition, role, and functioning of this body. Please provide this information.

MYLAN RESPONSE: The HEALTH CARE PROVIDER REGISTRATION: New Health Care Providers Registering with CPAS section of the program summary has been revised to clarify the role of the independent quality assurance committee and more clearly define the responsibility of CPAS regarding this committee. (See page 2 of the CPAS program summary provided in Attachment 2.) Specifically, this section has been revised as follows:



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- a. The text has been edited to strongly recommend the use of an independent quality assurance committee. The program recommends that the independent quality assurance committee should consist of individuals within the treatment community who are willing to oversee the proper prescribing and dispensing of clozapine.
- b. CPAS recommends that all access groups develop a treatment plan and provide this document to the independent quality assurance committee. The committee should oversee all facets of the plan to ensure good clinical practice by the access group.
- c. CPAS will contact both healthcare providers in response to any issues regarding monitoring compliance. Also, CPAS will provide an independent quality assurance committee any information regarding access group compliance issues upon request.

FDA COMMENT 2. TRACKING PATIENTS: WEEKLY AND BI-WEEKLY WBC MONITORING
(Physician Declares Patient "Interrupted Therapy")

The statement: "Any patient whose therapy has been interrupted must begin a new six month cycle of weekly WBC count monitoring" is true in the context of your definition of "interrupted therapy" on page 97, which requires that an abnormal blood event have occurred. However, using a broader definition, if the interruption in treatment was not related to a blood event, this would not be consistent with current labeling for clozapine products. Specifically, within the first six months of treatment, if there were no abnormal blood events and the treatment interruption was not longer than one month, the six month "clock" need not be reset. Also, after the first six months, if there were no abnormal blood events and the interruption was not longer than one year, biweekly monitoring may continue. The flowcharts on pages 113 and 115 do make this distinction between "interrupted therapy" and "break", respectively. Please make this distinction in the CPPP summary for clarity.

MYLAN RESPONSE: The summary of CPAS has been revised throughout the text to clearly define both "interrupted therapy" and "treatment break" and to distinguish the rules for resetting the monitoring "clock" based on the status of "interrupted therapy" and "treatment break".

"Treatment Break" has been added to the Definition of Terms within the program summary. A patient with a "treatment break" is defined as a patient whose treatment is suspended due to an event other than a clozapine induced abnormal blood event. The definition of "interrupted treatment" remains as an interruption in clozapine treatment due to a clozapine induced abnormal blood event. Specifically, an abnormal blood event that causes the WBC Count to drop below 3000/mm³ or the ANC value to drop below 1500/mm³. The revised CPAS program summary is provided in Attachment 2.

The following summary sections have also been revised to further clarify the difference between "treatment break" and "interrupted therapy":

- a. **PATIENT REGISTRATION: Patients with "Interrupted Treatment" Registration** (see page 4 of the program summary): This section has been edited to clarify the definition of "interrupted treatment" and to explain the resetting of the bi-weekly clock due to this status. Also, CPAS will confirm "interrupted treatment" status with the healthcare provider to ensure that the status is not actually related to a "treatment break".
- b. **TRACKING PATIENTS: WEEKLY AND BI-WEEKLY WBC MONITORING: Physician Declares Patient "Continuing Clozapine Treatment"** (see page 6 of the program summary) and **Physician Declares Patient "Interrupted Treatment"** (see page 7 of the program summary): These subsections have been edited to clarify the differences between "interrupted treatment" and "treatment break". In addition, the text was revised to clarify the program and monitoring stipulations related to a "treatment break" of greater than one month during the requisite six month weekly monitoring period, and a "treatment break" of greater than one year after the requisite six month period.
- c. **PARAMETERS FOR WEEKLY VS BI-WEEKLY MONITORING: Patients Continuing Clozapine Treatment Less than 6 Months** (see page 8 of the program summary): Text has been added to this section to clarify that the bi-weekly monitoring eligibility date will be reset to the first dispensing following a "treatment break" of greater than one month during the requisite six month weekly monitoring. The text was also revised to note that CPAS will commence administrative action if bi-weekly monitoring begins prior to the requisite 6 month period.

FDA COMMENT 3. Please describe your system for monitoring compliance with the CPPP and what action will be taken in instances of non-compliance.

MYLAN RESPONSE: The program summary has been revised to provide a section describing the system that will be used for monitoring compliance. The new compliance monitoring section appears on page 12 of the revised program summary provided in Attachment 2. This section also incorporates the use of the Questionable Dispensing Reports and Courtesy Reminders to notify the healthcare professional of an instance of non-compliance or potential non-compliance. These Reports and Reminders will constitute the first level of action taken in instances of non-compliance. The Questionable Dispensing Reports and Courtesy Reminders were described in the original CPPP summary provided in a February 12, 1999 amendment to the application and are provided in Attachment 5 for your reference. The compliance monitoring section in the program summary also describes the additional steps that will be taken in instances of non-compliance.

The system for monitoring compliance and actions taken in response to non-compliance are summarized as follows:

- a. System compliance will be monitored on multiple levels. As previously described, the CPAS database will provide notices to both the physician and pharmacist for certain package insert violations related to WBC Counts in the form of Questionable Dispensing Reports, and the system will provide Courtesy Reminders relative to certain potential package insert requirements.
- b. A copy of all transmissions occurring between the database system and the healthcare provider is sent to the CPAS Product Information Coordinator. Compliance issues outside of Questionable Dispensing Reports will be addressed similarly. If the issue is determined to be one of compliance, the Product Information Coordinator is notified.
- c. The Coordinator will contact both the physician and pharmacist to discuss the issue directly with the parties. The Product Information Coordinator will document all discussions through a Compliance Assessment Report.
- d. If the Product Information Coordinator determines that an actual violation has occurred after discussing the issue with the healthcare providers, the MYLAN Healthcare Provider Quality Assessment Committee will be provided a copy of the Questionable Dispensing Report, if applicable, and the completed Compliance Assessment Report. If the committee determines that another course of action must occur, the access group in question will be notified.
- e. Further action includes, but is not limited to the issuance of a formal written warning to all necessary parties, or withdrawal of Mylan clozapine prescribing or dispensing privileges. After a withdrawal of privileges, all wholesalers will be notified that the pharmacy status has been changed to ineligible. After the privileges of the pharmacy and/or physician have been withdrawn, it will be noted within the CPAS registry.

FDA COMMENT 4. Describe your plan for auditing the distribution of clozapine by wholesalers to pharmacies.

MYLAN RESPONSE: Mylan plans to distribute clozapine either directly to pharmacies or through wholesalers. If the product is distributed through wholesalers, the wholesaler must be registered with CPAS prior to receiving shipments of Mylan clozapine. Wholesalers register with CPAS by completing a Distribution Stocking Form (Form F). A copy of Form F is provided in Attachment 4. As a condition of registration, the wholesaler must agree that it will provide Mylan clozapine only to pharmacies registered with CPAS. CPAS will provide the registered wholesalers a list of registered pharmacies that may receive Mylan clozapine. In addition, CPAS will

provide the wholesalers a weekly list of newly registered pharmacies and a monthly list of all registered pharmacies.

If Mylan ships clozapine directly to the registered pharmacies, Mylan distribution centers will only be allowed to ship the product to those pharmacies registered with CPAS. A list of all registered pharmacies will be provided to the centers.

The CPAS program summary has been revised to provide a new section describing wholesaler registration and auditing. This new section appears on page 5 of the program summary provided in Attachment 2.

FDA COMMENT 5. Include absolute neutrophil count (ANC) criteria along with the WBC count criteria (i.e., your monitoring system, flow diagrams, etc.)

MYLAN RESPONSE: The absolute neutrophil count (ANC) criteria have been added to the flow diagrams that are provided in Attachment 3 and to the prescribing reminders on the reporting forms (Forms C and E) that are provided in Attachment 4. The absolute neutrophil count (ANC) criteria also remain on the Courtesy Reminders and Questionable Dispensing Report that are provided in Attachment 5.

FDA COMMENT 6. Please add a block for the patient's middle initial on your registration and reporting forms.

MYLAN RESPONSE: The registration form (Form B), white blood cell (WBC) count reporting form (Form C), and the multiple-patient white blood cell (WBC) count reporting form (Form D) have been revised to provide a block for the patient's middle initial. The patient specific white blood cell (WBC) count reporting form (Form E) was not revised to add blocks for the patient's initials because the patient information (patient initials, patient social security #, and patient reclearance code) will be pre-printed on the form by CPAS before it is sent to the healthcare provider. However, CPAS will include the patient's middle initial on this form. A copy of the revised forms are provided in Attachment 4.

FDA COMMENT 7. To ensure that adequate space has been provided and that information will be printed more clearly and legibly, please provide individual blocks for the patient's initials, social security number, etc., on your multiple patient WBC count reporting form.

MYLAN RESPONSE: The multiple-patient white blood cell (WBC) count reporting form (Form D) has been revised so that individual blocks are provided for the patient initials, social security number, physician DEA/ID, blood draw date, total WBC count, dosage, treatment status and weekly or biweekly WBC count reporting. A copy of this form is provided in Attachment 4.

- FDA COMMENT 8.** For traveling patients:
- a. You state that if no registered pharmacy is accessible, the physician may register with a pharmacy to form a protection group. How would the pharmacist be briefed about clozapine?

MYLAN RESPONSE: To the best of its abilities, CPAS will assist the access group to meet the needs of traveling patients, but maintains that prescribing and dispensing issues ultimately are the responsibility of the physician and pharmacist. To better address issues related to traveling patients, the **COVERING PHYSICIANS AND TRAVELING PATIENTS** section of the CPAS summary has been revised as follows (see page 11 of the program summary in Attachment 2):

- a. CPAS will provide the physician with multiple copies of a patient specific WBC Count Reporting Form (Form E). A copy of Form E is provided in Attachment 4. Form E may be used by the physician for weekly or bi-weekly reporting. It is the physician's responsibility to ensure proper patient care when a covering physician is involved.
- b. Physicians of patients needing refills while traveling may request a list of registered pharmacies within given geographic parameters. The physician and new pharmacy must create an access group, but neither signatures nor a new re-clearance code are necessary since both are already registered within the database.
- c. If a new pharmacy must be registered, CPAS will assist in the facilitation of this process upon request of the physician or pharmacy. CPAS will assist in finding a pharmacy in the vacation destination, contacting the pharmacist in-charge, and commencing dialogue regarding the patient's traveling situation. CPAS will express mail all registration, product information and educational program information to the pharmacy. In addition, the address for the system web site will be provided during the initial contact to provide a more rapid access to the package insert and an overview of clozapine and system requirements for pharmacies with Internet access.

- FDA COMMENT 8.** For traveling patients:
- b. Novartis indicates that they will express mail medication to patients unable to get it at the vacation site. Do you have similar plans?

MYLAN RESPONSE: Currently, Mylan does not have plans to express mail medication directly to patients at vacation sites. The access group pharmacy may air mail the supply to a pharmacy at the vacation location. CPAS will assist the access group in identifying potential pharmacies for shipment and will help with any coordination efforts necessary. Ultimately, it is the responsibility of the access group to resolve these issues. CPAS will only act as an advisory body during this time. Also, the emergency one week supply, per the package insert, may be used if necessary.

FDA COMMENT 9. For physicians and pharmacists new to clozapine, what methods/materials will Mylan use to orient them to the drug and CPPP?

MYLAN RESPONSE: Physicians and pharmacists who express an interest in Mylan's clozapine, whether or not they are new to clozapine, will be given an educational brochure that provides information about both clozapine and CPAS. All healthcare providers registered in CPAS will also be provided this brochure. A representative color print copy of the educational brochure is provided in Attachment 6. After the brochure was printed, additional textual changes were made in the brochure. Therefore, a copy of the revised script is also provided in Attachment 6.

FDA COMMENT 10. A phone number does not appear on any of the forms you submitted for review. How can a member of the protection group reach you with concerns or questions, especially if Internet access is not available? Will staff be available for emergencies?

MYLAN RESPONSE: All of the forms have been revised to provide CPAS's address, toll-free telephone number and toll-free fax number. Copies of the revised forms are provided in Attachment 4. Members of the access group can contact CPAS with concerns or questions by mail, internet, telephone, or facsimile. The educational brochure that is provided to every healthcare professional registered with CPAS also provides a section detailing how the healthcare provider can contact and communicate with CPAS.

Medical emergencies and adverse events will be handled by Mylan's Clinical department under the same procedures that are currently used to address medical emergencies and adverse events for Mylan's other products. Professionals in Mylan's clinical department are available 24 hours a day. CPAS will forward healthcare professionals to a professional in Mylan's Clinical department for these types of emergencies.

OTHER PROGRAM REVISIONS

In addition to revisions made to the program in response to the Agency's comments, Mylan has made the following changes in CPAS:

REVISION 1: Mylan revised the HEALTH CARE PROVIDER REGISTRATION: Health Care Providers Currently Registered with Another Manufacturer section of the CPAS summary (see page 3 of the program summary in Attachment 2) to provide a method whereby pharmacies who are currently dispensing another manufacturer's clozapine and is enrolled in a clozapine patient monitoring program, may obtain Mylan clozapine prior to registering an access group. This method is summarized as follows:

- a. By completing the CPAS Pharmacy Stocking Form (Form A), the pharmacy provides CPAS with all necessary information to determine eligibility for Mylan clozapine dispensing. The completed form clarifies that the pharmacy is currently dispensing clozapine tablets and is enrolled in a patient monitoring program of another manufacturer.

- b. Upon completion of the Pharmacy Stocking Form and acceptance by CPAS, all members of the distribution channel will be notified of the pharmacy acceptance. The pharmacy may now order supplies of Mylan clozapine from within the proper distribution channels, and dispense to "continuing treatment" patients, prior to registering as an access group.

REVISION 2: New capabilities within the CPAS database now allow physicians and pharmacists to report both weekly and bi-weekly WBC counts over the Internet. The program summary has been revised to reflect this change. (See **CPAS DATABASE PROCESSING: Physician and Pharmacist Internet Access** page 15 of the program summary in Attachment 2 and Internet Security and Web Site.) A summary of this change is as follows:

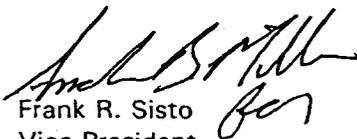
- a. Physicians and pharmacists will have the same access privileges within the database system. Both parties will now be able to report both weekly and bi-weekly reporting forms over the Internet.
- b. Database security is based on a layered system to reduce the potential of unauthorized individuals accessing the system. Also, digital ID's are used in association with 128 bit encryption to protect against breaches in confidentiality.

REVISION 3: Due to changes to the database and the need for clarity between "interrupted therapy" and a "therapy break", CPAS has eliminated the use of Questionable Dispensing Report (Report E). The elimination of the report is for clarification issues and does not imply a less stringent monitoring of the program.

REVISION 4: Due to changes to the database, the option of "Transferred Manufacturers" on the Reporting Forms and the Lot Number have been eliminated. The database will notify CPAS, through Courtesy Reminders and Questionable Dispensing Reports, of delinquent WBC Counts. Follow-up discussions with the healthcare providers will confirm that the patient was transferred to another manufacturer. Following this confirmation, the database will be updated to reflect the patient's status.

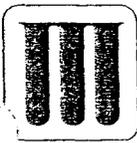
This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,


Frank R. Sisto
Vice President
Regulatory Affairs

FRS/abm

enclosures



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

APR 6 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

TELEPHONE AMENDMENT (CMC INFORMATION ENCLOSED)

RE: CLOZAPINE TABLETS, 25MG AND 100MG
ANDA #75-417
RESPONSE TO AGENCY TELEPHONE CALL OF APRIL 6, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to an April 6, 1999 telephone conversation with Dr. Paul Schwartz of your office regarding the review of our Clozapine Tablets, 25mg and 100mg ANDA #75-417.

Dr. Schwartz requested the following:

- 1) Revise the Assay and Content Uniformity procedures for the finished product to include the percent purity of the reference standard in the calculations.
- 2) Perform testing on the Clozapine drug substance.
- 3) Revise the in-process blend uniformity specifications to coincide with the Agency's current standard of % (mean of individual values) with an RSD of NMT %.

By way of this letter, Mylan acknowledges the Agency's requests and the following information is provided:

- 1) Revised procedures which include the reference standard percent purity as part of the calculations are provided in Attachment A.
- 2) Regarding n-butanol testing, and as briefly discussed with Dr. Schwartz, the ICH Guidance, Q3C Impurities: Residual Solvents, Section 3.4 pertaining to Analytical Procedures states: "If only Class III solvents are present, a nonspecific method such as loss on drying may be used." Accordingly, Mylan has obtained confirmation from the drug substance manufacturer that the only residual solvent that may be present in the finished drug substance is the Class III solvent, n-butanol. As indicated by the

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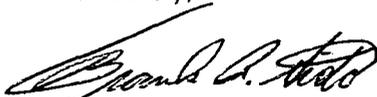
manufacturer, other solvents used in early stages of the manufacturing process are consistently removed from the material. Supportive information can be found in DMF Given the information provided in the ICH guidance and correspondence from the manufacturer (see Attachment B), Mylan continues to believe that the Loss on Drying test in conjunction with a limit of Not More Than % is appropriate to monitor residual solvents in the drug substance.

- 3) The in-process final blend specifications for Clozapine Tablets, 25mg and 100mg have been revised to include blend uniformity specifications of % (mean of individual values) with an RSD of NMT %. Mylan will routinely perform this test. The revised documents are provided in Attachment C.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

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MYLAN PHARMACEUTICALS INC

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FEB 12 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
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Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AB

BIOEQUIVALENCE AMENDMENT

RE: CLOZAPINE TABLETS, 25MG AND 100MG
ANDA #75-417
RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 19, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the January 19, 1999 correspondence pertaining to this application which was forwarded to Mylan from the Office of Generic Drugs' Division of Bioequivalence. In response to the January 19 correspondence, Mylan wishes to amend the application as follows:

A. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 1000 ml of 0.05 M Sodium acetate buffer at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test should meet the following specifications:

Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

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(304) 598-3232

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence has already been incorporated into Mylan's stability and quality control programs. This testing is identical to that which was previously proposed in the original ANDA for the above referenced product which was submitted on July 16, 1998.

It is also acknowledged and understood that the bioequivalency comments expressed in the correspondence dated January 19, 1999, are preliminary and may be revised after review of the entire application.

For your reference, a copy of the Agency correspondence dated January 19, 1999, is provided in Attachment 1.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

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SIGNED FDA FORM 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

MYLAN PHARMACEUTICALS INC.

DATE OF SUBMISSION

FEB 12 1999

TELEPHONE NO. (Include Area Code)

(304) 599-2595

FACSIMILE (FAX) Number (Include Area Code)

(304) 285-6407

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

781 CHESTNUT RIDGE ROAD
P.O. BOX 4310
MORGANTOWN, WV 26504-4310

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

75-417

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Clozapine

PROPRIETARY NAME (trade name) IF ANY

N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

5H-Dibenzo [b,e] [1,4] diazepine, 8-chloro -11-(4-methyl-1-piperazinyl)

CODE NAME (if any)

N/A

DOSAGE FORM:

Tablets

STRENGTHS:

25mg and 100mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE: Management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Clozaril® Tablets

Holder of Approved Application

Novartis Pharmaceuticals

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Response to Agency Correspondence Dated January 19, 1999

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

FEB 16 1999

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

ATTACHMENT 1

AGENCY CORRESPONDENCE DATED JANUARY 19, 1999



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 12 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/FA

**FACSIMILE AMENDMENT
(CMC INFORMATION ENCLOSED)**

RE: CLOZAPINE TABLETS, 25MG AND 100MG
ANDA #75-417
RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 19, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency which were provided to Mylan in a facsimile dated January 19, 1999. In response to the Agency's January 19, 1999 comments, Mylan wishes to amend this application as follows.

A. REGARDING CHEMISTRY ISSUES

Raw Material Controls - Active Ingredient:

FDA COMMENT 1. Please perform identification test A (melting point), heavy metals, tapped bulk density, and n-butanol testing as listed on the manufacturer's certificate of analysis. Establish the limits and provide them on your revised COA for the drug substance, clozapine. Also, revise your specification for assay per manufacturer's COA and include a complete name for CDD.

MYLAN RESPONSE: As requested by the Agency, Mylan has established tests and specifications for identification test A (melting point) and heavy metals. The specifications established for these tests have been adopted from the manufacturer, Mylan has also established a test and specification for tapped bulk density based on results obtained from in-house analyses. These tests have been incorporated into our Clozapine drug substance specifications and will be performed on each and every lot of drug substance prior to its release for use. Additionally, the assay specification has been tightened to % to match that of the manufacturer and a complete name for the impurity, has been included. Regarding the impurity, according to the ICH Guidance "Q3C Impurities: Residual Solvents", is classified as a Class III residual solvent. This guidance defines Class III Residual Solvents as "solvents with low toxic potential to man" and further states that "no health-based exposure limit is

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Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

GENERIC DRUGS

needed". Therefore, Mylan's Loss On Drying test is considered adequate to control any volatile matter present in the drug substance. The revised Clozapine specifications and certificates of analysis for Lot #RD6C006 used in the manufacture of the 25mg and 100mg tablets and Lot #8E109 also used in the manufacture of the 100mg tablet are provided in Attachment A and B, respectively. The assay procedure reflecting the revised limit and complete name for the impurity CDD is provided in Attachment C.

Manufacturing and Processing:

FDA COMMENT 2. Please clarify the size and number of samples that will be collected for blend uniformity testing. Also include the percent RSD value in your specification for the blend samples of clozapine tablets, 25mg and 100mg.

MYLAN RESPONSE: Regarding the size and number of samples to be collected for blend uniformity testing of Mylan's Clozapine Tablets 25mg and 100mg, a minimum of 30 samples will be collected from specified locations throughout the final blend. Each sample will represent the equivalent of 1 to 3 dosage units.

The In-Process Final Blend Specifications submitted in Mylan's ANDA #75-417 on pages 2972 and 2973 provide an acceptance criteria for both individual and average values. The individual values obtained from this testing must meet the USP requirements for Uniformity of Dosage Units <905> and, in addition, the average value of the blend uniformity samples must be within the range of % of the theoretical drug content.

Initially, ten blend samples are tested and, according to the USP criteria, the individual values must fall within the range of % of the theoretical drug content with a relative standard deviation of less than or equal to %. The USP further stipulates that if one sample of the 10 originally tested is outside the range of %, the remaining 20 samples should be tested and the following criteria applied: Not more than one sample of the 30 is outside the range of % and no sample is outside the range of % and the relative standard deviation of the 30 samples does not exceed %. Therefore, due to the possibility of different levels of testing with different percent RSD values, Mylan believes that reference to the USP requirements for Uniformity of Dosage Units <905> for acceptance criteria of individual values is sufficient. It should also be noted that this approach has been found acceptable in a number of recently approved Abbreviated New Drug Applications.

In response to the FDA's General Comment under labeling deficiencies regarding a scored tablet configuration, Mylan has added a score to our Clozapine 100mg tablet to match that of the innovator. In accordance with CDER's Manual of Policies and Procedures (MAPP 5223.2), "Scoring Configuration of Generic Products", the following documents are submitted in support of the revised tablet configuration:

- Revised Master Batch Records (exhibit and production size) reflecting the scored tablet configuration (refer to Page 12 of each Master Batch Record) are provided in Attachment D.
- The executed batch record for Clozapine Tablets, 100mg Lot #R1G0164 reflecting the manufacture of the scored tablet as well as packaging records, in-process data and a batch reconciliation is provided in Attachment E.
- Dissolution profiles comparing the scored and unscored tablet configurations are provided in Attachment F.
- The certificate of analysis for the scored Clozapine Tablets, 100mg Lot #R1G0164 is provided in Attachment G.
- Revised finished product specifications for Clozapine Tablets, 100mg reflecting the scored tablet description are provided in Attachment H.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA COMMENT 1. The FDA district laboratory will be performing methods validation on the new drug substance and the finished dosage form.

MYLAN RESPONSE: Mylan acknowledges that the FDA district laboratory will be performing methods validation on the new drug substance and the finished dosage form.

REGARDING LABELING ISSUES FROM THE AGENCY'S JANUARY 19, 1999 CORRESPONDENCE

As mentioned above, in response to the Agency's General Comment (#1) regarding a scored tablet configuration, Mylan has added a score to our Clozapine 100mg tablet to match that of the innovator (see above for supporting chemistry documentation).

In Agency Labeling Comment #4 (Patient Monitoring System) the Agency requested a more detailed description of Mylan's Clozapine Patient Protection Program (CPPP). Mylan's CPPP is presented in Attachment J. The presentation provides a textual summary describing the objectives of the program, the method through which health care providers and patients are registered into the program, the method used to track patients differentiating bi-weekly monitored from non-biweekly monitored patients, discontinuation procedures and CPPP database processing. Samples of the flowcharts, reporting forms, courtesy reminders and questionable dispensing reports are also provided in the Attachment J along with a description of the database design.

Mylan acknowledges that Novartis Pharmaceutical Corporation is maintaining a single national database of patients that should not be rechallenged with Clozapine. Accordingly, Mylan is in the process of developing a connection to this Novartis database and will appropriately incorporate the information into the CPPP database.

MYLAN RESPONSE: Regarding the labeling deficiencies described in Agency Comment#2 (Container)and Agency Comment #3 (Insert), Attachment L contains twelve (12) copies of the following final printed bottle labels and outsert for Clozapine Tablets, 25mg and 100mg:

BOTTLE LABELS

25mg

Code RM0825A - Bottles of 100 Tablets

100mg

Code RM0860A - Bottles of 100 Tablets

Code RM0860B - Bottles of 500 Tablets

OUTSERT

Code CLOZ:R1, Revised January 1999

The enclosed labeling incorporates the revisions requested in the Agency's letter of January 19, 1999. A copy of this correspondence is provided in Attachment I for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment K contains a side-by-side comparison of the final printed bottle labels to those previously submitted and Attachment L contains a side-by-side comparison of the final printed outsert (CLOZ:R1) to the outsert that was previously submitted. It is noted that prior to approval of this application, the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

As previously noted, a copy of the Agency correspondence dated January 19, 1999 is included in Attachment I, for the convenience of the reviewer.

Douglas L. Sporn
Page 5 of 5

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Handwritten signature of Frank R. Sisto in cursive script.

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/bad

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 30 1998

ORIG AMENDMENT

N/AB

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE BIOEQUIVALENCE AMENDMENT

RE: CLOZAPINE TABLETS, 25 MG AND 100 MG
ANDA #75-417
RESPONSE TO AGENCY TELEPHONE REQUEST OF OCTOBER 23, 1998

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to a October 23, 1998 telephone call from the Agency requesting additional long term frozen stability on clozapine in human plasma and an explanation regarding the analytical chromatograms for analysis of the plasma samples. Pursuant to the October 23 telephone request, Mylan wishes to amend this application with updated long term frozen stability and the requested explanation.

Study samples for the fasting (CLOZ-9722) bioequivalence study submitted in the referenced application were stored no more than 232 days at a nominal temperature of -70°C. Long-term frozen stability was initiated on March 10, 1998. At the time of submission of the bioequivalence studies, long-term frozen stability was an active, ongoing project with 56 days of frozen stability accumulated and reported in the analytical report. The analysis of long-term frozen stability was completed October 30, 1998, when 232 days of frozen stability had been accumulated. Stability is established for the frozen controls if the mean calculated concentrations are within ± 15% of the nominal value. Attachment 1 contains an addendum to the Clozapine Validation Report (Mylan Project #97-013-00) with validation tables demonstrating the frozen stability of clozapine for a period of 232 days when stored at a nominal temperature of -70°C.

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Douglas L. Sporn
Page 2 of 2

During the October 23, 1998, telephone call, the reviewer questioned why the representative blank plasma chromatograms on page 568 of the original ANDA had background peaks while the representative chromatograms for the clozapine standard (page 569 of the original ANDA) had little or no background noise. The differences seen between the two sets of chromatograms are a function of the intensity of electrical signal. The instrument used to quantitate clozapine utilizes automatic vertical scaling to display each chromatogram. In this processing mode the intensity of the largest scan, shown in the upper right corner of each chromatogram, is always displayed at full scale. The chromatograms shown on page 568 represent a matrix blank. The largest peaks in each scan window have intensities of 219 and 103 respectively. The chromatograms on page 569 represent the LOQ standard curve point and demonstrate scan intensities of 7,023 and 86,840 for the analyte and internal standard respectively.

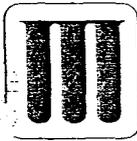
This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

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MYLAN PHARMACEUTICALS INC

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Office of Generic Drugs, CDER, FDA
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Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
AB

BIOEQUIVALENCE TELEPHONE AMENDMENT

RE: CLOZAPINE TABLETS, 25 MG AND 100 MG
ANDA #75-417
RESPONSE TO AGENCY TELEPHONE REQUEST OF OCTOBER 01, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above which is currently under review and to a October 01, 1998 telephone call from the Office of Generic Drugs' Division of Bioequivalence requesting a copy of the analytical method used in the analysis of plasma samples from the bioequivalence study (CLOZ-9722). In response to the phone call of October 01, Mylan wishes to amend the referenced application with the attached analytical method entitled *Method for the Determination of Clozapine in Heparinized Human Plasma Using Liquid-Liquid Extraction and High Performance Liquid Chromatography with Tandem Mass Spectrometric Detection.*

This amendment is submitted in duplicate. Should you have any questions regarding this submission, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

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R:\ANDA\CLOZAPINE\AGENCY-TELEPHONE-REQUEST-DATED_100198

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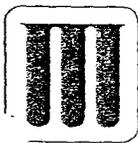
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MYLAN PHARMACEUTICALS INC

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JUL 16 1998

ELECTRONIC DATA ENCLOSED BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: CLOZAPINE TABLETS
25 MG AND 100 MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Clozapine

This application consists of a total of 19 volumes.

Archival Copy - 8 volumes.

Review Copy - 9 volumes.

Technical Section For Chemistry - 3 volumes.

Technical Section For Pharmacokinetics - 6 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a data diskette for the bioequivalence study conducted in support of this application.

This application provides for the manufacture of Clozapine Tablets, 25 mg and 100 mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

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[RDLIB.ANDA.CLOZAPINE]SECTIONS-01THRU07

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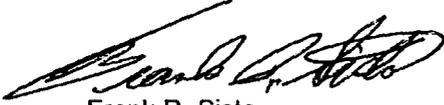
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Douglas L. Sporn
Page 2 of 2

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr