

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75417

ADMINISTRATIVE DOCUMENTS

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-417

Date of Submission: July 16, 1998

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Clozapine Tablets, 25 mg and 100 mg

Labeling Deficiencies:

1. GENERAL COMMENT

We note that your 100 mg tablet is not scored. Please be advised that because the 100 mg strength of the listed drug is scored, your scoring configuration should be the same. Please refer to CDER's Manual of Policy and Procedures (MAPP 5223.2) entitled "Scoring Configuration of Generic Drug Products" for guidance.

2. CONTAINER (25 mg - 100s; 100 mg - 100s, 500s)

Please ensure that the established name and strength are the most prominent information appearing on the label.

3. INSERT

a. WARNINGS (Agranulocytosis)

- i. Please ensure that the ultimate paragraph is contained within the same box as the rest of this subsection.
- ii. Revise the flow diagram so that the last box in the ultimate and penultimate rows read, "Weekly x 6 months" rather than " Weekly > 6 months".

b. PRECAUTIONS

i. Drug Interactions

Due to changes in the insert labeling of the reference listed drug (Clozaril - Novartis Pharmaceuticals; approved August 19, 1998), please revise to replace paragraph seven of

not to be rechallenged with clozapine. Please keep this in mind when developing your proposed system.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: (25 mg - 100s; 100 mg - 100s and 500s)

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Clozaril Tablets

NDA Number: 19-758

NDA Drug Name: Clozapine Tablets, 25 mg and 100 mg

NDA Firm: Novartis Pharmaceuticals Corporation

Date of Approval of NDA Insert and supplement #036:
August 19, 1998

Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).	x		
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
SCORING: Describe scoring configuration of RLD and applicant (page #) in the PTR			
Is the scoring configuration different than the RLD?	X		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (PTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: PTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Firm has been asked to score their 100 mg tablet to be the same as that of the innovator.
 2. The innovator packages its product in bottles of 100 and in unit dose packaging. Mylan is proposing to package its product in bottles of 100 and 500. Does the stability data support these packaging configurations?
-
-

FOR THE RECORD:

1. Labeling review based on the approved labeling for the listed drug (Clozaril - Novartis Pharmaceuticals Corporation; approved August 19, 1998).
2. Packaging
The innovator packages its products in bottles of 100 and in unit dose packaging.

Mylan is proposing to packaging its 25 mg product in round, beige, HDPE bottles of 100 with CRCs. The 100 mg product will be packaged in bottles of 100 and 500. The bottles of 500 will have a screw cap.

3. Labeling
Firm hs indicated that the drug name and strength will be differentiated by color.

Mylan provided a good description of their proposed monitoring system, however, did not provide samples of forms, depictions of flow diagrams, etc. They have been asked to submit a more detailed description which includes the above.

Since this product has been proposed in the PF, they have been asked to revise the DESCRIPTION section to use the second chemical name listed and to change the physical description of clozapine accordingly.

4. Inactive Ingredients
There does not appear to be a discrepancy in inactives between the DESCRIPTION section and the C&C statements.

5. USP Issues

This product has been proposed in the PF (Volume 24, No. 4).
It is recommended that clozapine tablets be preserved in well-closed containers.

RLD - Storage temperature should not exceed 86°F (30°C).

ANDA - Store at room temperature 15-30°C (59-86°F).

Dispense in a tight, light-resistant container as defined in the USP. Keep container tightly closed.

6. Bioequivalence Issues - Waiver granted 11/12/98.

7. Patent/Exclusivity Issues - None pending

Date of Review:
December 24, 1998

Date of Submission:
July 16, 1998

Primary Reviewer:

Date:

/S/
Team Leader:

12/28/98

/S/

Date:

12/29/98

cc:

ANDA: 75-417
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)

Review

Labeling Acceptable for Approval

John Mason 4/19/99

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-417

Date of Submission: February 12,
1999 (Amendment)

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Clozapine Tablets, 25 mg and 100 mg

Labeling Deficiencies:

1. CONTAINER (25 mg - 100s; 100 mg - 100s, 500s)

Satisfactory

2. INSERT

Satisfactory

3. MONITORING SYSTEM

The labeling of your proposed monitoring system as been forwarded to the Division of Neuropharmacological Drug Products (HFD-120) for review and comment. We will notify you when we receive their response.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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[Signature]
Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the PTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (PTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
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Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: PTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: ^M 4/19/99

The innovator packages its product in bottles of 100 and in unit dose packaging. Mylan is proposing to package its product in bottles of 100 and 500. Does the stability data support these packaging configurations?

FOR THE RECORD:

1. Labeling review based on the approved labeling for the listed drug (Clozaril - Novartis Pharmaceuticals Corporation; approved August 19, 1998; acknowledged and retained December 7, 1998).
2. Packaging
The innovator packages its products in bottles of 100 and in unit dose packaging.

Mylan is proposing to packaging its 25 mg product in round, beige, HDPE bottles of 100 with CRCs. The 100 mg product will be packaged in bottles of 100 and 500. The bottles of 500 will have a screw cap.

3. Labeling
The drug name and strength is differentiated by color, red for the 25 mg product and green for the 100 mg.

Mylan provided an excellent, very detailed description of their monitoring program. It has been consulted to HFD-120.

Since this product has been proposed in the PF, they revised the DESCRIPTION section to use the second chemical name listed and to change the physical description of clozapine accordingly per request.

4. Inactive Ingredients
There does not appear to be a discrepancy in inactives between the DESCRIPTION section and the C&C statements.
5. USP Issues
This product has been proposed in the PF (Volume 24, No. 4). It is recommended that clozapine tablets be preserved in well-closed containers.
RLD - Storage temperature should not exceed 86°F (30°C).
ANDA - Store at room temperature 15-30°C (59-86°F).
Dispense in a tight, light-resistant container as defined in the USP. Keep container tightly closed.

6. Bioequivalence Issues - Waiver granted 11/12/98.

7. Patent/Exclusivity Issues - None pending

Date of Review:
March 24, 1999

Date of Submission:
February 12, 1999

Primary Reviewer:

Date:

/S/

Team Leader:

Date:

/S/

3-25-1999

cc:

ANDA: 75-417
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)

Review

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 14, 1999

FROM: Thomas Laughren, M.D. 
Acting Deputy Director
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Response to Consult Request

TO: OGD
HFD-600

Background Information:

Issue Requiring Response: Clozapine distribution/WBC
monitoring program for ANDA 75-
417

Underlying Documents: Clozapine distribution/WBC
monitoring program for ANDA 75-
417

Date of Request: 4-1-99

Requester: Harvey Greenberg

Attached Response:

Attached to this memo is the Division's response to your consult request.

CC:
HFD-120/Consult File
HFD-120/TLaughren

DOC: HFD-600.01

Patent and Exclusivity Search Results from query on 019758 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

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[Patent and Exclusivity Terms](#)

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