

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**75417**

**CHEMISTRY REVIEW(S)**

## ANDA APPROVAL SUMMARY

<b>ANDA:</b> 75-417	<b>CHEMIST:</b> Neeru B. Takiar	<b>DATE:</b> April 19, 1999
<b>DRUG PRODUCT:</b> Clozapine		
<b>FIRM:</b> Mylan Pharmaceuticals Inc.		
<b>DOSAGE FORM:</b> Tablets	<b>STRENGTH:</b> 25 mg and 100 mg	
<b>cGMP:</b> EER was found acceptable on October 02, 1998.		
<b>BIO:</b> Bio study was acceptable by C.Kim on February 23, 1999.		
<b>VALIDATION - (Description of dosage form same as firm's):</b> The DS and DP are not covered by monographs in the USP. Method verifications performed by the FDA District Laboratory were satisfactory.		
<b>STABILITY:</b> The firm has provided satisfactory 3 months accelerated and 24 months room temperature stability data for both strengths (25 mg and 100 mg tablets). The stability data support an expiration period of 24 months.		
<b>LABELING:</b> Labeling was found acceptable by L. Golson on March 24, 1999.		
<b>STERILIZATION VALIDATION (if applicable):</b> N/A		
<b>SIZE OF BIO BATCH (Firm's source of NDS ok?):</b> Size of the bio batch for 25 mg and 100 mg is                      tablets. The drug substance was manufactured by                      and found acceptable by NBT on April 19, 1999.		
<b>SIZE OF STABILITY BATCHES (if different from bio batch, were they Manufactured via the same process?):</b> Size of stability batch is same as that of the bio batch.		
<b>PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:</b> Size of the proposed production batch size for 25 mg and 100 mg is                      Tablets. The manufacturing process is identical to the exhibit batch.		
<b>Signature of chemist:</b>  NBT 5/31/99 Neeru B. Takiar	<b>Signature of supervisor:</b>  PS Paul Schwartz, Ph.D. 4/19/99	



12. RELATED IND/NDA/DMF(s):

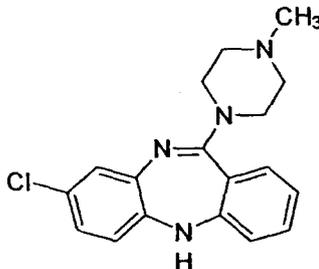
<u>DMF#</u>	<u>Type</u>	<u>Product</u>	<u>DMF holder</u>
		Clozapine	
		Stear-O-Wet M	
		75 cc Bottles	
		Resin	
		200 cc Bottles	
		Resin	
		CR Closure	
		Closure	
		Polypropylene	
		Petrothene®	
		Cotton	
		Cotton	

13. DOSAGE FORM: Tablet

14. POTENCY: 25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE:

Clozapine. 5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-. C<sub>18</sub>H<sub>19</sub>ClN<sub>4</sub>. 326.83. 5786-21-0. Sedative. USAN 1993, page 164.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: N/A

18. CONCLUSIONS AND RECOMMENDATIONS: The application is approvable.

19. REVIEWER: Neeru B. Takiar  
Endorsed by P. Schwartz, Ph.D.

DATE COMPLETED: 04/19/99

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Chem. Review # 2

JAN 19 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-417

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Clozapine Tablets, 25 mg and 100 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

*Raw Material Controls - Active Ingredient:*

1. Please perform identification test A (melting point), heavy metals, tapped bulk density, and 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.

*Manufacturing and Processing:*

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, 25 mg and 100 mg.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. The FDA district laboratory will be performing methods validation on the new drug substance and the finished dosage form.

Sincerely yours,

JSI

Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**OFFICE OF GENERIC DRUGS**

**ABBREVIATED NEW DRUG APPLICATION**  
**CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

1. **CHEMISTRY REVIEW NO.#** 1

2. **ANDA #** 75-417

3. **NAME AND ADDRESS OF APPLICANT:**

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

4. **LEGAL BASIS FOR SUBMISSION:**

Reference listed drug:

Clozaril® Tablets, 25 mg & 100 mg

NDA Nos: N19758 001 and 002 (Sep 26, 1989)

Manufacturer: Novartis Pharmaceuticals Corporation.

The firm certifies that, in its opinion and to best of its knowledge, Clozaril® is not covered by any patents or exclusivity provisions.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Clozapine

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Applicant:

07-16-1998 Date of application

FDA:

07-17-1998 Acceptable for filling

08-11-1998 ANDA Acceptance letter

10. **PHARMACOLOGICAL CATEGORY:** For management of severely ill schizophrenic patients.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**

<u>DMF#</u>	<u>Type</u>	<u>Product</u>	<u>DMF holder</u>
		Clozapine	
		Stear-O-Wet M	
		75 cc Bottles	

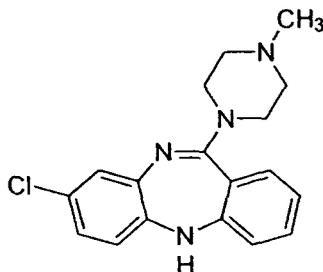
Resin  
 200 cc Bottles  
 Resin  
 CR Closure  
 Closure  
 Polypropylene  
 Petrothene®  
 1  
 Cotton  
 Cotton

13. **DOSAGE FORM:** Tablet

14. **POTENCY:** 25 mg and 100 mg

15. **CHEMICAL NAME AND STRUCTURE:**

Clozapine. 5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-. C<sub>18</sub>H<sub>19</sub>ClN<sub>4</sub>. 326.83. 5786-21-0. Sedative. USAN 1993, page 164.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

The following sections are *NOT SATISFACTORY*:

23. Raw material - active ingredient

26. Manufacturing and Processing

The following Section is *PENDING*:

32. Labeling

18. **CONCLUSIONS AND RECOMMENDATIONS:**

The application is not approvable. A Fax NA will issue.

19. **REVIEWER:** Neeru B. Takiar

**DATE COMPLETED:** 11/30/98

Endorsed by P. Schwartz, Ph.D.

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Chem Review #1