

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**75417**

**BIOEQUIVALENCY REVIEW(S)**

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA # 75-417

SPONSOR: Mylan Pharmaceuticals, Inc.

DRUG & DOSAGE FORM: Clozapine Tablets, USP

STRENGTH (S): 25 mg and 100 mg

TYPE OF STUDY: SD SDF MULT OTHER X

STUDY SUMMARY: N/A

Response is acceptable.

PRIMARY REVIEWER: Carol Y. Kim BRANCH: 3  
INITIAL: CS DATE: 2/23/99

TEAM LEADER: Barbara M. Davit BRANCH: 3  
INITIAL: BS DATE: 2/23/99

DIRECTOR  
DIVISION OF BIOEQUIVALENCE  
INITIAL: DK DATE: 2/25/99

DIRECTOR  
OFFICE OF GENERIC DRUGS  
INITIAL: \_\_\_\_\_ DATE: \_\_\_\_\_

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75417

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Clozapine Tablets, USP, 25 mg and 100 mg

The Division of Bioequivalence has found your response of February 12, 1999 to the Bioequivalence Amendment to be acceptable. The Division has no further questions at this time.

Sincerely yours,



Dale P. Conner, Pharm. D.  
Director  
Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Clozapine Tablets, USP  
25 mg and 100 mg  
ANDA #75417  
Reviewer: Carol Y. Kim  
v:\new\firmam\mylan\ltrs&rev\75417SA.299

Mylan Pharmaceuticals, Inc.  
Chestnut Ridge Road  
Submission Date:  
February 12, 1999

### Amendment Review

#### Background:

The firm submitted a Bioequivalence Amendment in response to Division of Bioequivalence comment in agency's correspondence, dated January 19, 1999. The bioequivalency comments are as follows:

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.

#### Firm's response:

Dissolution testing requested by DBE has already been incorporated into Mylan's stability and quality control programs.

#### Comment:

DBE acknowledged the firm's response acceptable.

#### Recommendation:

DBE has no further questions at this time.

*IS/*  
Carol Y. Kim, Pharm.D.  
Division of Bioequivalence  
Review Branch III

RD INITIALLED BY BDAVIT  
FT INITIALLED BY BDAVIT

Concur: *IS/*  
Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence

*B7ND 2/23/99*  
*IS/*  
Date: 2/23/99

Date: 2/25/99

OFFICE OF GENERIC DRUGS  
**DIVISION OF BIOEQUIVALENCE**

ANDA # 75-417

SPONSOR: Mylan Pharmaceuticals, Inc.

DRUG & DOSAGE FORM: Clozapine Tablets, USP

STRENGTH (S): 25 mg and 100 mg

TYPE OF STUDY:      SD X      SDF      MULT      OTHER

STUDY SUMMARY:

Formulation is acceptable, waiver is granted

~~SD~~ In a single-dose fasting bioequivalence study, Clozapine tablets, 25 mg, USP were shown to be bioequivalent to clozaril tablets.

PRIMARY REVIEWER: Carol Y. Kim  
INITIAL: CS

BRANCH: 3  
DATE: 11/1/98

TEAM LEADER: Barbara M. Davit  
INITIAL: BS

BRANCH: 3  
DATE: 11/5/98

DIRECTOR  
DIVISION OF BIOEQUIVALENCE  
INITIAL: AK

DATE: 11/12/98

DIRECTOR  
OFFICE OF GENERIC DRUGS  
INITIAL: \_\_\_\_\_

DATE: \_\_\_\_\_

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75417

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Clozapine Tablets, USP, 25 mg and 100 mg

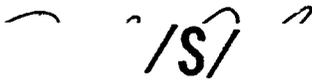
The Division of Bioequivalence has completed its review and has no further questions at this time.

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 80% (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.

Sincerely yours,



Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

CC: ANDA #75417  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-658/ Reviewer C. Kim

Endorsements: (Final with Dates)  
HFD-658/ Reviewer C. Kim *CK 11/1/98*  
HFD-658/ Bio team Leader B. Davit *BMD 11/5/98*  
HFD-617/ Project Manager  
HFD-650/ D. Conner *DC 11/12/98*

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 07/16/98

1. Fasting Study (STF)

Clinical:  
Analytical: Mylan Pharmaceuticals, Inc.

Strength: <sup>02-OCT-98  
30-OCT-98</sup> 25 mg  
Outcome: AC

2. DISSOLUTION WAIVER (DIW)

Clinical:  
Analytical: Mylan Pharmaceuticals, Inc.

Strength: ~~25 mg~~ &  
100 mg  
Outcome: AC

3. Study Amendment

*02 - OCT - 98*  
*30 - OCT - 98*

Strength: ~~25 mg~~ &  
~~100 mg~~ *all*  
Outcome: AC

Outcome Decisions: AC - Acceptable

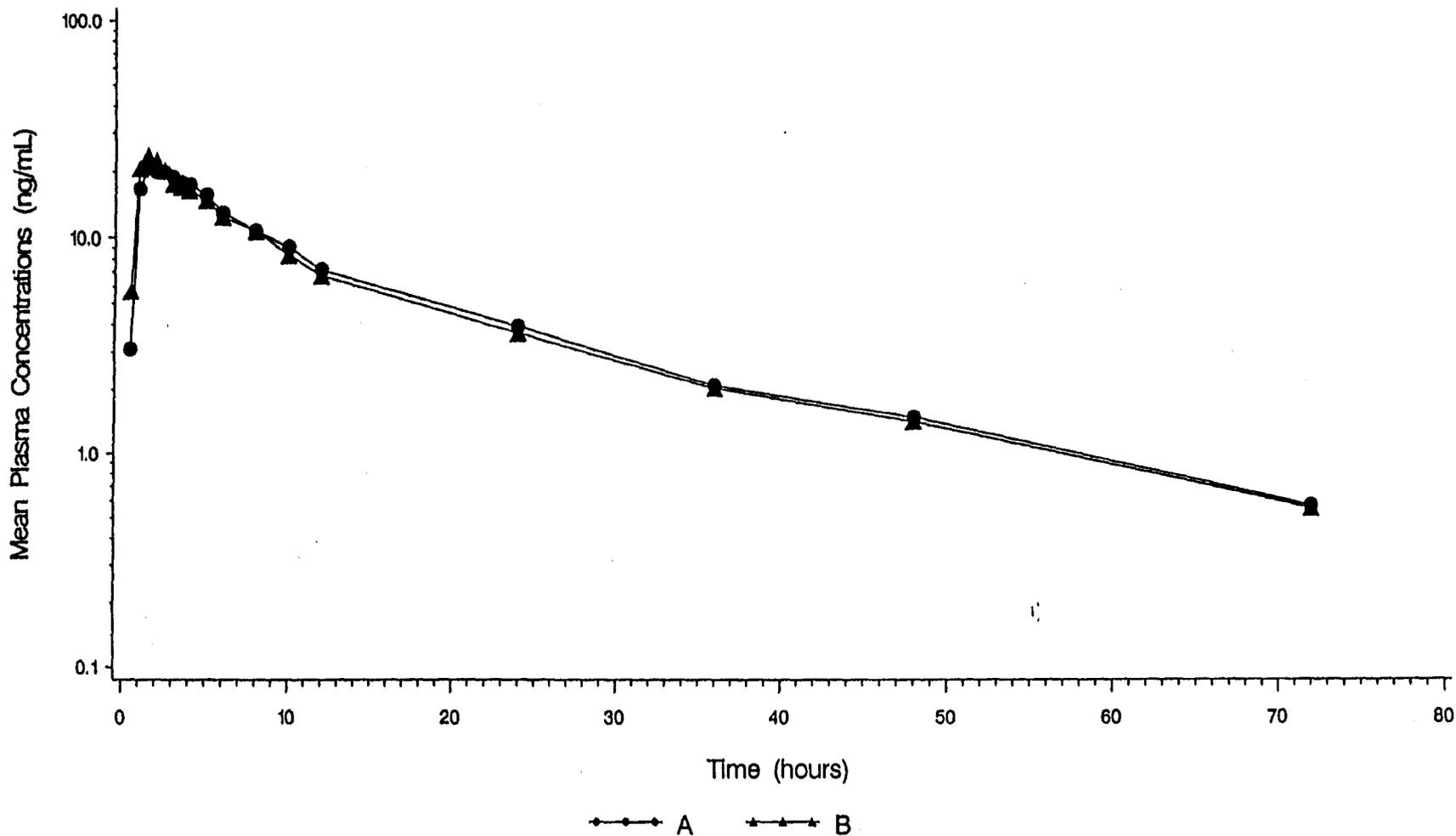
WinBio Comments: Fasting Study -Acceptable  
Dissolution -Acceptable

# CLOZAPINE (CLOZ-9722)

Total Dose: 12.5 mg (1/2x25mg Tablet), Study Type: Fasting

Mean Clozapine Plasma Concentrations

N= 34



Treatment A is A (Clozaril #152X9130)

Treatment B is B (Clozapine #2C005C)

**Clozapine Tablets, USP**  
25 mg and 100 mg  
ANDA #75417  
Reviewer: Carol Y. Kim

**Mylan Pharmaceuticals, Inc.**  
Chestnut Ridge Road  
Submission Date:  
July 16, 1998  
October 2, 1998  
October ~~30~~, 1998

## **Review of a Bioequivalence Study and Dissolution Data**

### **I. Introduction**

**Class:** Atypical antipsychotic agent

**RLD:** Clozaril<sup>®</sup> Tablets, 25 mg (Sandoz Pharmaceuticals)

**Recommended Dose:** Initial dose- 25 mg/day, Target dose- 300-450 mg/day

### **II. Objectives**

Review of:

- Two-way crossover in vivo bioequivalence study comparing Mylan's Clozapine Tablets 25 mg strength, to Sandoz Pharmaceuticals' Clozaril<sup>®</sup> Tablets, 25 mg strength, following administration of a 12.5 mg dose (one half tablet) under fasting conditions.
- Dissolution data for 25 mg and 100 mg tablets.
- A waiver request for 100 mg tablets.

### **III. Background**

Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about % of an orally administered dose reaches systemic circulation unchanged. Gastrointestinal absorption appears to occur principally in small intestine and is approximately % complete within 3.5 hours after an oral dose. Food does not appear to affect the systemic bioavailability of clozapine. Clozapine is approximately % bound to serum proteins. It is almost completely metabolized prior to excretion and only trace amounts (2-5%) of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces; maximum fecal excretion has been estimated at 38%. The derivatives are the metabolized products seen in urine and feces. The metabolite has only limited pharmacological activity, while the derivatives are inactive.

**IV. Protocol No. CLOZ-9722: A single-dose, 2-way crossover randomized study under fasting conditions:**

**A. Study information**

**Study facility information:**

Clinical Site:

Investigator:

Analytical Site:

Analytical Director:

Study Dates:

Analysis Dates:

Storage Period:

Mylan Pharmaceuticals Inc., Morgantown, WV.

Michael Adams

September 9, 1997 – November 14, 1997

March 24, 1998 to May 13, 1998

no > 232 days at -70°C

**Study design:**

Protocol No.:

CLOZ-9722

Design Type:

two-way crossover

Randomized:

Y

Single or Multiple dose:

single

No. of Treatment:

2

No. of Periods:

2

No. of Sequences:

2

Washout Period:

7 days

**Subjects:**

Normal Healthy Volunteers:

Y

IRB Approval:

Y

Informed Consent

Y

No. of Subjects Enrolled:

Entered: 41 males

Completed: 34 males

Age:

18-50 years

Inclusion/Exclusion Criteria:

listed in vol: 1.2, pages 3-4

Housing:

Evening prior to each drug administration until minimum of 48 hours after dosing.

**Treatment information:**

Treatment:

A

B

Test or Reference:

Reference

Test

Product Name:

Clozaril<sup>®</sup> Tablet

Clozapine Tablet

Strength:

25 mg

25 mg

Manufacturer:

Sandoz Pharmaceuticals

Mylan Pharmaceuticals

|                    |  |                                      |
|--------------------|--|--------------------------------------|
| Lot No.:           | #152X9130 (25 mg)<br>#2D007H (12.5 mg) | #2C005C (25 mg)<br>#2D006H (12.5 mg) |
| Expiration Date:   | 01/1999                                | TBE                                  |
| Content Uniformity | %                                      | %                                    |
| Assay:             | %                                      | %                                    |
| Dose Administered: | 12.5 mg (1/2 X 25 mg)                  | 12.5 mg (1/2 X 25 mg)                |
| Length of Fasting: | 10 hours                               | 10 hours                             |
| Batch Size:        | Clozapine 25 mg and 100 mg-            | tablets                              |

**Dosing:**

Subjects fasted at least 10 hours prior to and 4 hours after dosing. Each oral dose was administered with 240 ml of water. Standard meals were provided at 4 and approximately 10 hours after dosing.

**Blood Sampling:**

|                     |   |
|---------------------|---|
| Blood sample volume | 10 ml   |
| No. of time points  | 17  |
| Time points:        | 0 and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 24, 36, 48, 72 hours post dose |

The plasma blood samples were stored at -70°C until analysis

**B. Study Results**

**1. Clinical**

Drop-outs: Subject #11 was discontinued during period 1 due to adverse events requiring treatment. The severity of reaction was reported to be moderate and probably drug related. Subject #4, #27, #32, and #33 were discontinued prior to period 2 due to transient asymptomatic leucopenia (<1500 ANC). Subject #34 was withdrawn from the study prior to period 2 because of personal reasons that were not study related. Subject #38 was withdrawn from the study because he received treatment B twice.

Adverse events: Fifteen adverse events (9 subjects) were reported in this study. Of those, two were reported as possibly drug related, and thirteen were reported as probably drug related. A total of five adverse events were reported as moderate and ten events were reported as mild reaction. (vol. 1.3, table 2, page 1180) The common adverse events were neutropenia, bradycardia, and hypotension.

**2. Analytical Analysis (The following section is not to be released under FOI)**

Method:

Internal Standard:

Specificity:

Linearity:

(Standard curve samples)

|                               |       |                  |  |
|-------------------------------|-------|------------------|--|
| Quality Control (QC) Samples: | High: | ng/ml            |  |
|                               | Mid:  | ng/ml            |  |
|                               | Low:  | ng/ml            |  |
| Precision of Standards:       |       | % CV             |  |
| Precision of QC Samples:      |       | % CV within run  |  |
|                               |       | % CV between run |  |
| Accuracy of Standards:        |       | %                |  |
| Accuracy of QC Samples:       |       | % within run     |  |
|                               |       | % between run    |  |

Stability in Plasma:

Freeze-thaw: 3 cycles

Pre-extraction at RT: 4 hours

Processed sample stability at RT: 96 hours

Long term at -70°C: 232 days

Recovery:

Low QC (0.75 ng/ml): %

High QC (15 ng/ml): %

Internal Standard: %

Reassays:

Protocol Deviations:

Y (see vol 1.3, p. 1178)

Conclusion:

Analytical method is acceptable

### 3. Pharmacokinetic/Statistical Analysis

Mean Clozapine plasma levels of 34 subjects are summarized in Table 1.

Table 1: Mean Clozapine Plasma Concentrations following an oral dose of 12.5 mg (1/2 of 25 mg) for test and reference products (N=34)

| Time (hour) | Test<br>Lot# 2C005C |        | Reference<br>Lot # 152X9130 |        | Ratio |
|-------------|---------------------|--------|-----------------------------|--------|-------|
|             | Mean (ng/ml)        | CV %   | Mean (ng/ml)                | CV %   | T/R   |
| 0.00        | 0.00                | -      | 0.00                        | -      | 0     |
| 0.50        | 5.72                | 112.20 | 3.10                        | 138.68 | 1.85  |
| 1.00        | 20.70               | 69.64  | 16.67                       | 100.59 | 1.24  |
| 1.50        | 23.72               | 42.76  | 20.89                       | 58.55  | 1.14  |
| 2.00        | 22.52               | 37.72  | 20.10                       | 47.91  | 1.12  |
| 2.50        | 20.17               | 39.01  | 19.87                       | 48.46  | 1.02  |
| 3.00        | 17.58               | 36.29  | 18.97                       | 39.58  | 0.93  |
| 3.50        | 17.07               | 36.64  | 17.88                       | 36.15  | 0.95  |
| 4.00        | 16.45               | 39.23  | 17.49                       | 39.79  | 0.94  |
| 5.00        | 14.88               | 44.05  | 15.68                       | 44.39  | 0.34  |
| 6.00        | 12.44               | 40.71  | 13.01                       | 39.53  | 1.16  |
| 8.00        | 10.73               | 41.91  | 10.76                       | 40.97  | 0.99  |
| 10.00       | 8.42                | 42.91  | 9.10                        | 44.56  | 0.93  |
| 12.00       | 6.79                | 49.37  | 7.20                        | 42.03  | 0.94  |
| 24.00       | 3.71                | 51.88  | 3.99                        | 52.50  | 0.93  |
| 36.00       | 2.06                | 66.02  | 2.12                        | 68.75  | 0.97  |
| 48.00       | 1.43                | 73.69  | 1.50                        | 72.79  | 0.95  |
| 72.00       | 0.56                | 89.62  | 0.57                        | 97.62  | 0.98  |

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for Clozapine are shown in Table 2. The LS means of the non-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2: Test mean/Reference mean ratios of Clozapine pharmacokinetic parameters

| Parameter*       | Test Mean | CV % | Ref Mean | CV % | Ratio (T/R) <sup>1</sup> |
|------------------|-----------|------|----------|------|--------------------------|
| AUCI             | 316       | 44.5 | 323      | 43.6 | 0.98                     |
| AUCT             | 296       | 44.0 | 302      | 42.3 | 0.98                     |
| C <sub>MAX</sub> | 28.1      | 37.1 | 28.4     | 46.5 | 0.99                     |
| KE               | 0.0431    | 40.0 | 0.0418   | 34.6 | 1.03                     |
| T <sub>½</sub>   | 18.2      | 31.7 | 18.5     | 35.1 | 0.98                     |
| T <sub>MAX</sub> | 1.94      | 61.3 | 2.19     | 55.3 | 0.89                     |

\*AUCT=ng\*hr/ml, AUCI=ng\*hr/ml, T<sub>MAX</sub>=hr, C<sub>MAX</sub>=ng/ml

<sup>1</sup>Calculated by reviewer



**V. Dissolution**

|                       |   |
|-----------------------|---|
| Method of dissolution | USP 23, Apparatus I (basket)                                  |
| Speed                 | 100 rpm   |
| No. of Units Tested   | 12  |
| Medium                | 0.05 M Sodium Acetate Buffer, pH 4.0                          |
| Temperature           | 37°C  |
| Volume                | 1000 ml   |
| Specifications        | NLT % (Q) is dissolved in 45 minutes                          |
| Assay Methodology     |   |
| Reference Product     | Sandoz's Pharmaceuticals' Clozaril <sup>®</sup> Tablet, 25 mg |

**Result of dissolution profile summary for Clozapine 25 mg, 100 mg and 12.5 mg (half tablet)**

| Sampling Times (minutes) | Mylan Lot # 2C005C Strength: 25 mg |         |     | Clozaril <sup>®</sup> Lot # 152X9130 Strength: 25 mg |         |     | Mylan Lot # 2C006C Strength: 100 mg |         |     | Clozaril <sup>®</sup> Lot # 336X9353 Strength: 100 mg |         |     |
|--------------------------|------------------------------------|---------|-----|--|---------|-----|-------------------------------------|---------|-----|---|---------|-----|
|                          | Mean %                             | Range % | %CV | Mean %   | Range % | %CV | Mean %                              | Range % | %CV | Mean %  | Range % | %CV |
| 15                       | 98                                 |         | 1.0 | 100  |         | 1.2 | 94                                  |         | 1.7 | 40  |         | 9.7 |
| 30                       | 100                                |         | 1.3 | 103  |         | 1.2 | 95                                  |         | 1.1 | 77  |         | 6.2 |
| 45                       | 98                                 |         | 1.2 | 100  |         | 1.2 | 95                                  |         | 1.9 | 98  |         | 2.2 |
| 60                       | 100                                |         | 1.2 | 103  |         | 1.0 | 97                                  |         | 1.7 | 98  |         | 2.6 |

| Sampling Times (minutes) | Mylan Lot # 2C005C Strength: 12.5 mg (1/2 tablet) |         |     | Clozaril <sup>®</sup> Lot # 152X9130 Strength: 12.5 mg (1/2 tablet) |         |     |
|--------------------------|---|---------|-----|---|---------|-----|
|                          | Mean %  | Range % | %CV | Mean %  | Range % | %CV |
| 15                       | 98  |         | 1.0 | 102   |         | 2.4 |
| 30                       | 99  |         | 1.6 | 103   |         | 2.5 |
| 45                       | 99  |         | 1.2 | 103   |         | 2.7 |
| 60                       | 99  |         | 1.5 | 103   |         | 2.6 |

**Comment**

The firm conducted dissolution according to the procedure described in the OGD guidance (11/15/96 version). The dissolution data are acceptable.

**VI. Formulation Comparison**

**Comparison of Formulation for Mylan's Clozapine 25 mg tablet vs. 100 mg tablet:  
full batch size million tablets (Not to Be Released Under FOI)**

| Strength                                   | 25 mg         |   | 100 mg        |   |
|--|---------------|---|---------------|---|
|  | Mg per tablet | % | Mg per tablet | % |
| ✓ Clozapine                                |               |   |               |   |
| <b>Inactive Ingredients</b>                |               |   |               |   |
| ✓ Colloidal Silicon                        |               |   |               |   |
| ✓ Dioxide, NF                              |               |   |               |   |
| ✓ Magnesium Stearate/Sodium Lauryl Sulfate |               |   |               |   |
| ✓ Lactose Monohydrate, NF                  |               |   |               |   |
| ✓ Microcrystalline Cellulose, NF           |               |   |               |   |
| ✓ Crospovidone, NF                         |               |   |               |   |
| ✓ FD&C Red #40 Lake                        |               |   |               |   |
| ✓ FD&C Blue #2 Lake                        |               |   |               |   |
| Total theoretical weight                   |               |   |               |   |

**Reference Formulations of Clozaril<sup>®</sup> (Not to Be Released Under FOI)**

| Strength           | 25 mg | 100 mg |
|--------------------|-------|--------|
| <b>Ingredients</b> |       |        |
| Clozapine          | mg    | mg     |
| Magnesium Stearate | mg    | mg     |
| Silicon Dioxide    | mg    | mg     |
| Talc               | mg    | mg     |
| Povidone           | mg    | mg     |
| Starch             | mg    | mg     |
| Lactose            | mg    | mg     |

### Assay and Content Uniformity

| Product  | Assay % | Content Uniformity (%CV) |
|--|---------|--------------------------|
| Test, Clozapine 25 mg Tablets, Lot # 2C005C        |         |                          |
| Reference, Clozapine 25 mg Tablets, Lot # 152X9130 |         |                          |

### **VII. Waiver Request**

1. The firm requested a waiver for the 100 mg tablets.
2. Two test formulations, Clozapine 25 mg & 100 mg tablet, are not exactly proportional but similar. The proportions of vary between the two formulations. Total tablet weight is the same for both strengths. Moreover, the dissolution profile of Clozapine 25 mg is comparable to that of Clozapine 100 mg.
3. The dissolution profiles differ for the 25 mg and 100 mg strengths of the RLD, Clozaril<sup>®</sup>. However, both strengths pass the specifications. Note that the formulations differ for the two strengths of the innovator's product.
4. Based on the acceptable in vivo bioequivalence and in vitro dissolution data conducted by the firm on its Clozapine Tablets, 12.5 mg (1/2 of tablet), 25 mg strength, lot # 2C005C and 100 mg strength, lot # 2C006C, the waiver for the 100 mg strength tablets of the test product is granted.

### **VIII. Recommendations**

1. The single-dose bioequivalence study #CLOZ-9722 under fasting conditions, conducted by Mylan Pharmaceuticals on its Clozapine Tablet, USP, 12.5 mg (1/2 tablet), 25 mg, lot #2C005C, comparing it to Clozaril<sup>®</sup> 12.5 mg (1/2 tablet), 25 mg, lot # 152X9130, manufactured by Sandoz Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Clozapine Tablet, USP, 25 mg is bioequivalent to Sandoz Pharmaceuticals' Clozaril<sup>®</sup> Tablet, 25 mg.
2. The dissolution method conducted by Mylan Pharmaceuticals on its Clozapine Tablets, 12.5 mg (1/2 tablet), 25 mg, lot # 2C005C and 100 mg, lot # 2C006C, is acceptable.
3. The waiver of in vivo bioequivalence study requirements for the 100 mg strength tablets of the test product is granted based on 21 CFR 320.22 (d) (2).

4. Mylan Pharmaceuticals' Clozapine Tablets, 100 mg strength, are deemed bioequivalent to Sandoz Pharmaceutical's Clozaril<sup>®</sup>, 100 mg tablets.
5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 1000 ml of acetate buffer at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test should meet the following specification:

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

The firm should be informed of the recommendations.

*1*  
*/S/*  
Carol Y. Kim, Pharm.D.  
Division of Bioequivalence  
Review Branch III

RD INITIALLED BY BDAVIT  
FT INITIALLED BY BDAVIT,

*8729 10/30/98*

*/S/*

Date: 11/5/98

Concur:

*/S/*

Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence

Date: 11/12/98