Revised
NOV 15 1996

GUIDANCE[1,2]

CLOZAPINE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Clozapine, a dibenzodiazepine derivative, with potent antipsychotic properties, is an atypical neuroleptic drug, because, unlike other neuroleptics, it does not appear to produce significant extrapyramidal side effects (1, 2). Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment (3). Clozapine has been reported to be effective in a substantial portion (30-50%) of schizophrenic patients who are refractory to or intolerant of classic antipsychotic therapy. Despite its promising therapeutic potential, the relatively high incidence of clozapine-induced agranulocytosis (1 to 2% of patients) is a major factor restricting wide use of the drug in psychiatric practice (4). Although the exact pharmacological mechanism of action of clozapine is not fully understood, the drug does possess significant binding affinity for different dopamine receptors, with recent evidence supporting binding to the D_4 receptor sub-type (5). The drug also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors.

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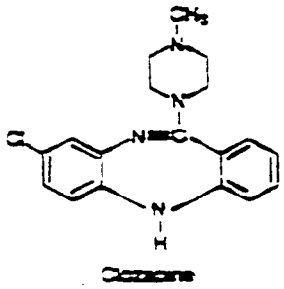
1 Although this guidance document, prepared by the Office of Generic Drugs, does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration or the public, it does represent the agency's current thinking on clozapine bioequivalence studies. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-594-2290; Fax: 301-594-0181).

2 The Office of Generic Drugs has received reports of **cardiovascular adverse reactions** in subjects participating in clozapine bioequivalence studies. A medical consultant to the office is available to provide information about ways to prevent and, if they occur, manage these adverse reactions. Prior to initiating a clozapine bioequivalence study, sponsors are encouraged to contact the Division of Bioequivalence, Office of Generic Drugs, at 301-594-0350, to obtain assistance in contacting this consultant.

Currently, clozapine is marketed by Sandoz Pharmaceuticals Corporation under the name Clozaril®, 25 mg (scored) and 100 mg tablets. The drug may be administered without regard to meals. In order to minimize the risk of agranulocytosis, Clozaril® (clozapine) is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication. For initial treatment with Clozaril® (clozapine), it is recommended that treatment begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-400 mg/day by the end of 2 weeks. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to 600-900 mg/day range to obtain an acceptable response.

B. Chemistry

Clozapine [8-Clair-11-(4-methyl-1-piperazinyl)-5H-dibenzo [1,4] diazepine] is a tricyclic dibenzodiazepine derivative. The structural formula is:



Clozapine occurs as a yellow, crystalline powder and is very slightly soluble in water. Commercially available clozapine tablets should be stored in tight containers at a temperature not exceeding 30°C.

C. Pharmacokinetics

Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27-50% of an orally administered dose reaches systemic circulation unchanged. Gastrointestinal absorption appears to occur principally in small intestine and is approximately 90-95% complete within 3.5 hours after an oral dose. Food does not appear to affect the systemic bioavailability of clozapine. The relative oral bioavailability of commercially available 25 mg and 100 mg clozapine tablets reportedly is equivalent relative to a clozapine solution. Following oral administration of

a single 25 mg or 100 mg oral dose of clozapine as tablets in healthy adults, the drug is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours. Peak plasma concentrations may be delayed with higher single doses and with multiple dosing of the drug (6).

The decline of plasma clozapine concentrations in humans is biphasic. The elimination half-life of clozapine following a single 75 mg or 100 mg oral dose reportedly averages 8 hours (range: 4-12 hours). The elimination half-life of clozapine at steady state following administration of 100 mg twice daily reportedly averages 12 hours (range: 4-66 hours). Steady-state plasma concentrations of clozapine are achieved after 7-10 days of continuous dosing (6). In a multiple-dose study, a dose of 100 mg twice daily, produced an average steady state peak plasma concentration of 319 ng/mL (range: 102-771 ng/mL), at about 2.5 hours (range: 1-6 hours). The average minimum concentration at steady state administered the same dose was 122 ng/mL (range: 41-343 ng/mL).

Considerable interindividual variations in plasma clozapine concentrations have been observed in patients receiving the drug, and some patients may exhibit either extremely high or extremely low plasma concentrations with a given dose. Such variability may occur at high dosages (e.g., 400 mg daily) of the drug. There is some evidence that interindividual differences in pharmacokinetic parameters for clozapine may result, at least in part, from nonlinear, dose-dependent pharmacokinetics of the drug. However, a linear dose-concentration relationship also has been reported (6). Results of a study in patients with chronic schizophrenia revealed a correlation between oral clozapine doses of 100-800 mg daily and steady-state plasma concentrations of the drug. In addition, linearly dose-proportional changes in area under the plasma concentration-time curve (AUC) and in peak and trough plasma concentrations have been observed with oral dosage of 37.5, 75, and 150 mg twice daily in other studies (7).

Clozapine is approximately 95% bound to serum proteins. Clozapine is almost completely metabolized prior to excretion and only trace amounts 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. The desmethylated, hydroxylated, and N-oxide derivatives are the metabolized products seen in urine and feces. The desmethyl metabolite has only limited pharmacological activity, while the hydroxylated and N-

oxide derivatives are inactive.

II. *IN VIVO* BIOEQUIVALENCE STUDIES[3]

A. Product Information

1. FDA Designated Reference Product: Clozaril® 25 mg and 100 mg tablets manufactured by Sandoz Pharmaceuticals Corporation. Clozaril® 25 mg is available as scored tablet.

2. Batch size: The test batch or lot should be manufactured under production conditions and should be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Study (a Fasting Single Dose or Multiple Dose Bioequivalence Study)

Clinical studies in healthy subjects and patients have revealed that clozapine-treated individuals at times experience orthostatic hypotension and severe bradycardia. In one study of 17 clozapine naive normal volunteers administered 25 mg. of clozapine, 10 subjects experienced orthostatic hypotension and 8 experienced bradycardia below 40 beats per minute (2 of these 8 experienced sinus arrest and 1 required a chest thump to restore normal sinus rhythm.) In another study involving 9 normal volunteers administered 25 mg. of clozapine, 4 subjects experienced bradycardia with cardiac pauses as long as 5 to 7 seconds. Information about these events was previously made available by the Food and Drug Administration on January 31, 1995. The proposed study protocols are designed to reduce the likelihood of these events or, should they occur, to assure that adequate treatment is available. The following two protocols may be considered:

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[3] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

1. A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions comparing equal 12.5 mg (one-half of a 25 mg tablet) doses of the test and reference products, to be conducted in healthy subjects.

2. A steady-state, multiple-dose, random, two-period, two-treatment, two-sequence crossover study comparing equal doses of the test and reference products, to be conducted in schizophrenic patients who are receiving a stable dose of clozapine.

Details of each protocol are provided in the following sections of the guidance.

1. Fasting Single Dose Bioequivalence Study in Healthy Volunteers

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when administered equal doses, as labeled.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with a washout period between Phase I and Phase II of at least 5 days. An equal number of subjects should be randomly assigned to each of the two possible dosing sequences. Before the study is initiated, the proposed protocols should be approved by an Institutional Review Board (IRB).

Facilities: All subjects should be confined in an area with adequate facilities to treat possible adverse effects such as bradycardia and hypotension. All subjects should have continuous cardiac monitoring (i.e. telemetry) for a minimum of 12 hours post-dosing. The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors. Equipment, medication and personnel required for cardiac or respiratory resuscitation should be readily available at the facility.

Selection of Subjects: The applicant should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 30-35 subjects be used in this study. Subjects should be healthy volunteers between the

ages of 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical testing. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

See Page 7 for Precautions and Safety Issues

Precautions and Safety Issues:

a. Subjects should be free of any history of vasovagal syncope.

b. To reduce likelihood of a vasovagal reaction, it is recommended that subjects receive the drug in the late morning(e.g., 9 or 10 am) after they have been ambulatory for several hours as opposed to very early in the morning.

c. Subjects should remain in the supine position for the first six hours after dosing to minimize the chances of orthostatic hypotension and syncope.

d. Blood pressure and pulse rates should be measured in the supine position just prior to dosing and at 15-minute intervals for 0 - 2 hours post-dosing, at 30-minute intervals for 2 - 6 hours post-dosing and then at hourly intervals for the remainder of the observation period. Additional blood pressure and pulse rate measurements should be obtained if the clinical situation justifies it (e.g., hypotension, dizziness, adverse symptoms thought to be of cardiovascular etiology).

e. Subjects should be confined for at least 12 hours after dosing.

f. Subjects should be adequately hydrated. This may be achieved by administering 240 ml of water before the overnight fast, 240 ml of water one hour before dosing, 240 ml of water with the study dose, and 240 ml of water every two hours for six hours post dosing.

g. Intravenous access should be maintained for at least six hours after dosing.

h. Subjects should be adequately informed of possible cardiovascular adverse effects in the consent form.

Subject Education

All subjects should be advised by the investigator or knowledgeable medical personnel about the risk for orthostatic hypotension and syncope associated with the use of clozapine. The information provided to the subjects should address the following topics.

a. the risk of fainting and slow heart rate associated with clozapine.

b. the mechanism believed to be responsible for the occurrence of fainting (i.e., fall in blood pressure particularly with sitting or standing).

c. the activities or positions that can precipitate fainting with clozapine.

d. the prodromal symptoms that may occur prior to fainting, such as weakness, feeling of warmth, nausea, dizziness, and sweating.

e. the actions to be taken if prodromal symptoms develop.

In any study involving the use of clozapine in healthy subjects, the investigator and the sponsor have primary responsibility to guarantee that adequate precautions are taken during the trial to ensure the safe conduct of the study. This responsibility includes providing adequate informed consent with regard to serious adverse events that may occur during the course of the study.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose (12.5 mg, one-half of 25 mg tablet) of the test or reference product with 240 ml of water. Each 12.5 mg half-tablet should be weighed, and its weight should be within $\pm$5% of the other half for both test and reference products.

Restrictions: Study volunteers should be subject to the following restrictions:

a. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

b. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

c. Subjects should take no Rx medications beginning two weeks and no OTC medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0 and 72.0 hours post-dose. Plasma/serum should be separated promptly and immediately frozen until assayed. Following five days washout period, subjects should begin Study Phase Two.

2. Multiple Dose Study in Patients Receiving a Stable Dose of Clozapine.

Design: The study design is multiple dose, steady-state, two-treatment, two-period, two-sequence crossover. Patients should be receiving a stable daily dose of clozapine administered in equally divided doses at 12 hour intervals. According to the randomization schedule, an equal number of patients will receive either the test (Treatment "A") or reference (Treatment "B") drug product in the same dose as administered prior to the study every 12 hours for seven days. Blood sampling will occur over an interdose interval on Day 7, with additional samples collected in the days preceding Day 7 to confirm steady state conditions. Before the study begins, the proposed protocols should be approved by an Institutional Review Board.

Facilities: Patients should meet entry health criteria as determined by physical examination, medical history and routine hematologic and biochemical tests. All patients should be admitted to an in-patient facility prior to receiving the first study dose and remain until completion of the study. Blood pressure, heart rate, and body temperature should be monitored during the study. The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Procedures: Patients should be administered Study Treatment "A" or "B" in the same dose as the therapeutic dose administered prior to the study twice daily at fixed 12 hour intervals with 240 ml of water for seven days. For those patients receiving 100 mg tablets, since the 100 mg tablet is not scored, the tablet should not be split by other means.

Restrictions: Study patients should be subject to the following restrictions:

a. Patients should fast for at least eight hours prior to and four hours after the administration of the morning dose of the test or reference treatment in each period on Day 7 (i.e., the days on which blood samples are to be collected to assess the area under the concentration-time curve). All Day 7 meals should be standardized during the study.

b. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

c. No xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Patients with CNS depression or comatose states, history of myeloproliferative states, history of severe drug-induced granulocytopenia or agranulocytosis, severe renal or hepatic disease, uncontrolled epilepsy, the need for concurrent use of another drug known to suppress bone marrow functioning, taking any known enzyme inducers or inhibitors known to influence clozapine plasma levels should be excluded from the study.

Blood Sampling (Multiple Dose): Venous blood samples should be collected after the Day 7 morning dose to assess the interdose area under the concentration-time curve at pre-dose (0 hours) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0. The pre-dose blood sampling must include at least three successive trough level samples (C_{min}). These samples should be collected on the last two days of dosing in each period to ensure that steady-state blood plasma/serum levels

are achieved in each study period. There is no washout period between period I and period II. Thereafter patients should be restarted on their usual dose of medication and discharged from the study.

C. Analytical, Statistical and Other Recommendations

Analytical Methods: Clozapine should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curves and Q.C. chromatograms, should be submitted for one-fifth (20%) of the subjects, chosen at random. The applicant should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum): See the Office's Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

Clinical Report and Adverse Reactions: Subject or patient medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

Retention of Samples: The laboratory conducting the bioequivalence testing should retain an appropriately identified reserve samples of the test product and the reference standard used to perform an *in vivo* bioequivalence study for approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information on retention of bioequivalence samples, please refer to 21 CFR 320.32.

III. *IN VITRO* TESTING CRITERIA

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*. The current official USP dissolution method should be followed, if available, and should be referenced by the applicant. The following method and tolerances are currently recommended for this

product:

Apparatus:	USP 23 apparatus 1 (basket)
RPM:	100
Medium:	Acetate buffer pH 4.0
Volume:	1000 mL
Sampling Times:	15, 30, 45 and 60 minutes
Tolerance (Q):	NLT 80% in 45 minutes
Analytical:	As per USP 23, if available, or UV absorbances @ ca. 290 nm

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots (whole and half tablet for the 25 mg strength if 12.5 mg dose is used in the bioequivalence study) should be performed as described in USP 23 if available.

IV. WAIVER REQUIREMENTS

A. Waiver of *in vivo* bioequivalence study requirements for the 25 mg and/or the 100 mg strength of the generic product may be granted per 21 CFR 320.22(d)(2) provided both of the following conditions are met:

1. The strength (for which waiver is requested) is proportionally similar in both active and inactive ingredients to the strength which has been demonstrated to be bioequivalent to the corresponding reference product *in vivo*.

2. The 25 mg and the 100 mg strengths of the generic products meet the dissolution testing criteria.

V. REFERENCES

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4. Fitton A, Heel RC. Clozapine a review of its pharmacological properties, and therapeutic use in schizophrenia. Drugs 1990;5:722-25.

5. Jann MW, Grimsley SR, Gray EC, Chang W-H. Pharmacokinetics and pharmacodynamics of clozapine. Clin. Pharmacokinet 1993;24:161-15.

6. American hospital formulary service drug information'92. Bethesda, Maryland: American Society of Hospital Pharmacists, 1992:1270-11.

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Concur: _____ Date: K.15.96

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