Guidance for Industry

Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Revision I

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I. INTRODUCTION

This guidance provides recommendations for sponsors of abbreviated new drug applications (ANDAs) designing bioequivalence studies for generic clozapine products. This document revises the recommendations provided in a guidance on the same topic issued in November 1996. In the 1996 guidance, the Agency recommended that doses of clozapine tablets be administered to healthy subjects as well as to the appropriate patient population in bioequivalence studies for generic clozapine products. Because a high number of healthy subjects experienced serious adverse effects such as hypotension, bradycardia, syncope, and asystole during clozapine bioequivalence studies, FDA is recommending that studies not be conducted using healthy subjects. In addition, a single-dose study using a 12.5 mg dose is no longer recommended. Instead, this guidance recommends a multiple-dose bioequivalence study conducted in patients using the highest dosage strengths (e.g., 100 mg tablets).

The protocols described in this guidance are designed to reduce the likelihood of adverse events or, if adverse events should occur, to ensure that adequate treatment is available.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Clozapine, a dibenzodiazepine derivative with potent antipsychotic properties, is indicated for the management of patients with severe schizophrenia who fail to respond adequately to standard

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration.

antipsychotic drug treatment. A significant risk of agranulocytosis and seizures associated with its use is a major factor restricting wide use of clozapine in psychiatric practice.

The FDA recommends that treatment with clozapine begin with one-half of a 25 milligram (mg) tablet (12.5 mg) once or twice daily and that treatment be continued with daily dosage increments of 25-50 mg per day, if well tolerated, to achieve a target dose of 300 to 400 mg per day by the end of 2 weeks. While many patients respond adequately at doses between 300 and 600 mg per day, it may be necessary to raise the daily dose to between 600 and 900 mg to obtain an acceptable response. Dosing should not exceed 900 mg per day.

In humans, clozapine from 25 mg and 100 mg tablets is equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg twice a day, the average steady-state peak plasma concentration occurs at an average of 2.5 hours (range 1-6 hours) after dosing. Food does not appear to affect clozapine systemic bioavailability. The mean elimination half-life of clozapine after a single 75 mg dose is 8 hours (range 4-12 hours), compared to a mean steady-state half-life of 12 hours (range 4-66 hours) following 100 mg twice a day dosing. The elimination half-life increases significantly upon multiple dosing relative to single-dose administration, raising the possibility of concentration dependent pharmacokinetics. However, at steady-state, linearly dose-proportional changes have been observed in AUC, peak, and minimum clozapine plasma concentrations after administration of 37.5 mg, 75 mg, and 150 mg (twice daily).

Orthostatic hypotension with or without syncope can occur with clozapine treatment. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur with the first dose. Due to the hypotensive effects associated with administration of clozapine to healthy subjects, the original recommendations in a guidance on clozapine tablets published in November 1996 are being changed. This document revises and supersedes the previous version of the guidance. The Agency currently recommends that steady-state studies to evaluate the bioequivalence of clozapine products be performed only on patients who are already receiving an established maintenance dose of an approved clozapine product and have failed to respond adequately to standard antipsychotic drug treatment. The Agency believes that the previously recommended study design using half tablets in healthy subjects was adequate to establish bioequivalence of generic clozapine products; however, the safety concerns associated with the use of clozapine in healthy subjects are significant, and it is recommended that this practice not be continued.

III. IN VIVO STUDIES

A. Product Information

1. FDA Designated Reference Product

Applicants may consult FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* for the appropriate reference product.

2. Batch size

The test batch or lot should be manufactured under production conditions and should be at least 10% of the size 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. Steady-State Bioequivalence Study

The objective of this steady-state bioequivalence study is to compare the rate and extent of absorption of a generic formulation with a reference formulation when administered at equal doses, as labeled.

Potential sponsors should consider the following study design. This study is appropriate for institutionalized or noninstitutionalized patients. Procedures should be in place to ensure medication compliance in either setting.

1. Steady-State Study in Patients Receiving a Stable Dose of Clozapine

The study would be conducted in patients who are receiving a stable daily dose of clozapine administered in equally divided doses at 12-hour intervals. Patients who are receiving multiples of 100 mg every 12 hours would be eligible to participate in the study of the 100 mg strength by continuing their established maintenance dose. According to the randomization schedule, an equal number of patients would receive either the generic formulation (Treatment A) or the reference formulation (Treatment B) in the same dose as administered prior to the study every 12 hours for 10 days.

Patients would then be switched to the other product for a second period of 10 days. No washout period is necessary between the two treatment periods. After the study is completed, patients could be continued on their current dose of clozapine using an approved clozapine product as prescribed by their clinicians.

2. Procedures for the Study

Before the study begins, the proposed protocol must be approved by an institutional review board (IRB).[2]

The FDA recommends that applicants enroll a sufficient number of patients to ensure adequate statistical power.

[2] See 21 CFR 314.94(a)(7)(iii).

Patients should receive study treatment A or B with 240 milliliters (ml) of water at fixed 12-hour intervals for 10 days, using multiples of the 100 mg strength.

Blood samples should be collected over a dosing interval on day 10, following preliminary sampling on days 7, 8, and 9 to confirm steady-state conditions. The last dose of clozapine to be taken before blood sampling for each period should be administered at the clinical site to assure exact timing of sampling.

3. Patient Entry Criteria and Facilities

To enter into this study, patients should be appropriate candidates for clozapine therapy (as stated in product labeling) and have been taking a stable dose of clozapine for at least three months. Patients should be otherwise healthy as determined by physical examination, medical history, and routine hematologic and biochemical tests.

Outpatients should be hospitalized for at least 2 days during the collection of each set of pharmacokinetic samples. The clinical and analytical laboratories used for the study should be identified in the study report, along with the names, titles, and curriculum vitae of the medical and scientific/analytical directors.

4. Safety Monitoring

White blood cell (WBC) counts should be monitored and clozapine treatment modified, if necessary, in accordance with the agranulocytosis warning in the labeling of the reference listed drug product. Patients requiring modification of clozapine treatment should be dropped from the study and provided with prompt medical care. Blood pressure, heart rate, and body temperature should be monitored during the study and immediate medical care provided for any significant abnormalities.

5. Restrictions

Patients should fast for at least 8 hours prior to and 4 hours after the administration of the morning dose of the test or reference treatment on day 10 of each period (i.e., the days on which blood samples are to be collected to assess the concentration-time curve). All meals on day 10 should be standardized during the study.

Water may be allowed, except for 1 hour before and 1 hour after drug administration, when no liquid should be permitted other than that needed for drug dosing.

Patients with any of the following should be excluded from the study:

- A history of allergic reactions to clozapine or other chemically related psychotropic drugs

- Concurrent primary psychiatric or neurological diagnosis, including organic mental disorder, severe tardive dyskinesia, or idiopathic Parkinson’s disease

- A total white blood cell count below 4000/ml, or an absolute neutrophil count below 2000/ml

- A history of granulocytopenia or myeloproliferative disorders (drug-induced or idiopathic)

- Significant orthostatic hypotension (i.e., a drop in systolic blood pressure of 30 mm Hg or more and/or a drop in diastolic blood pressure of 20 mm Hg or more on standing)

- Concurrent use of antihypertensive medication or any medication that might predispose to orthostatic hypotension

- A medical or surgical condition that might interfere with the absorption, metabolism, or excretion of clozapine

- A history of epilepsy or risk for seizures

- Concurrent use of other drugs known to suppress bone marrow function

- Expected changes in concomitant medications during the period of study

- Positive tests for drug or alcohol abuse at screening or baseline

- A history of alcohol or drug dependence by *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* criteria during the 6-month period immediately prior to study entry

- Compliance with outpatient medication schedule not expected

- History of multiple syncopal episodes

6. Blood Sampling

Venous blood samples should be collected after the day 10 morning dose to assess the concentration-time curve at predose (0 hours) and at 0.25, 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 hours. The predose blood sampling should include at least three successive trough level samples (C_{min}). These samples should be collected on the last 3 days of dosing in each period to ensure that steady-state blood plasma/serum levels are achieved in each study period.

C. Other Recommendations

1. Precautions and Safety Issues

- Patients should be confined for at least 12 hours after the first dose of the test and reference products.

- Patients should remain in the supine position for the first 6 hours after the first dose, even if they were previously on a stable dose of clozapine.

- Patients 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 2 hours for 6 hours post-dosing.

- Patients must be adequately informed of possible cardiovascular adverse effects in the consent form.[3]

2. Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum)

The following pharmacokinetic data should be used for the evaluation of bioequivalence of the multiple dose study:

- Individual and mean blood drug concentration levels

- Individual and mean trough levels (C_{min} ss)

- Individual and mean peak levels (C_{max} ss)

- Calculation of individual and mean steady-state $AUC_{interdose}$ ($AUC_{interdose}$ is AUC during a dosing interval at steady-state)

- Individual and mean percent fluctuation [$=100 * (C_{max}\ ss - C_{min}\ ss)/C_{average}\ ss$]

- Individual and mean time to peak concentration

The log-transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and Cmax) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The trough concentration data should also be analyzed statistically to verify that steady-state was achieved prior to Period 1 and Period 2 pharmacokinetic sampling.

[3] See 21 CFR 50.25.

3. Clinical Report and Adverse Reactions

Patient medical histories, physical examination and laboratory reports, and all incidents of possible adverse reactions should be reported.

IV. IN VITRO TESTING CRITERIA

A. Dissolution Testing

Dissolution testing on 12 dosage units of the test product versus 12 units of the reference product should be conducted for all strengths. The lot used in the biostudy should be used for dissolution testing as well. The United States Pharmacopeia (USP) method is recommended for this product. Sampling times of 15, 30, 45 and 60 minutes are recommended.

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, the coefficient of variation (relative standard deviation), and similarity comparisons of dissolution profiles (f2 calculations) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in the latest edition of the USP.

V. WAIVER REQUIREMENTS

Waiver of in vivo bioequivalence study requirements for the lower strengths of a generic product can be granted if the following conditions are met:[4]

1. The in vivo study on the 100 mg tablet is acceptable.
2. The strengths are proportionally similar in active and inactive ingredients to the strength tested in vivo.
3. All strengths meet an appropriate in vitro dissolution test.

[4] See 21 CFR 320.22(d)(2)