Contains Nonbinding Recommendations

Guidance on Clozapine[1]

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Active ingredient: Clozapine

Form/Route: Tablets/Oral

Recommended studies: 1 study

1. Type of study: Steady-state
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 100 mg
   Subjects: 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. FDA recommends that studies not be conducted using healthy subjects.
   Additional Comments: 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

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Analytes to measure (in appropriate biological fluid): Clozapine in plasma.

Bioequivalence based on (90% CI): Clozapine

Waiver request of in-vivo testing: 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 100 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12

[1] These recommendations were issued as a final guidance in June 2005 and moved to Individual Product Bioequivalence Recommendations in March 2011.

dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Additional comments regarding the bioequivalence study:

Before the study begins, the proposed protocol must be approved by an institutional review board (IRB).[1]

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

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.

1. 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.

2. 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.

3. 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

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

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

4. 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.

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.[2]

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)

[2] See 21 CFR 50.25.

- 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. Clinical Report and Adverse Reactions

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