

Draft Guidance on Clozapine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Clozapine

Dosage Form; Route: Suspension; oral

Recommended Studies: One study

1. Type of study: Steady-state
Design: Two-treatment, two-way crossover *in-vivo*
Strength: 50 mg/mL

Subjects: Patients who are at steady-state for three months prior to entry into the BE study on a stable once daily evening dose of an approved clozapine drug product (ideally Versacloz Oral Suspension). Patients should continue their established maintenance once daily evening dose throughout the study. FDA recommends studies not be conducted using healthy subjects.

Additional Comments: According to the BE randomization schedule, an equal number of patients will receive either the test generic oral suspension formulation (Treatment A) or the reference formulation (Treatment B) in the same dose and dosing interval as administered prior to the study. Patients entering the study will be stable and at steady state on a once daily evening dose of an approved clozapine drug product. At study entry, patients will be placed on either the reference drug or the test product in a once daily evening dose for the first 10 days of the study. Patients will switch to the other treatment product for the second period of 10 days at the same once daily evening dose. No washout period is necessary between the two treatment periods. After the study is completed, patients may continue on their current dose of clozapine using an approved clozapine product prescribed by their clinicians.

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

Bioequivalence based on (90% CI): Clozapine

Waiver request of in-vivo testing: N/A

Dissolution test method and sampling times:

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Please note that a dosage unit for a suspension is the labeled strength (mL). A total of 12 units from 12 different bottles should be used. 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 24-hour intervals for 10 days before crossing over to the other product. The patient should receive the same strength of clozapine once daily in the evening that he or she was stabilized on before the study.

In each treatment period, 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 treated with a stable dose and a once daily (evening) dosing interval of an approved clozapine product (ideally Versacloz Oral Suspension) for at least three months prior to study entry. 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

¹ See 21 CFR 314.94(a)(7)(iii).

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.

Absolute neutrophil counts (ANC) should be measured through routine blood draws to monitor and modify (if indicated) clozapine treatment, according to Section 5.1 Severe Neutropenia in Versacloz labeling. Patients whose ANC levels fall below 1000/ μ L require interruption of clozapine treatment, will be dropped from the study, and provided with prompt medical care in accordance with Section 5.1. Blood pressure, heart rate, and body temperature will 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 5 hours after the administration of the evening 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 1000/ μ L
- A history of neutropenia or myeloproliferative disorders (drug-induced or idiopathic)
- Patients with benign ethnic neutropenia (BEN)
- 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) or syncope
- 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
- Patients who are HIV positive
- Caffeine intake was greater than 500 mg/day

4. Blood Sampling

Venous blood samples should be collected after the day 10 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, 12.0, 16.0, and 24.0 hours. After the 5.0-hour sample and 12.0-hour sample, the patients receive a light meal. The pre-dose blood sampling should be collected after the evening dose 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 $AUC_{\text{interdose}}$ ($AUC_{\text{interdose}}$ is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [$=100 * (C_{\max,ss} - C_{\min,ss})/C_{\text{average,ss}}$]
- Individual and mean time to peak concentration ($T_{\max,ss}$)

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 C_{\max}) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The

² See 21 CFR 50.25.

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.