Contains Nonbinding Recommendations

Guidance on Clozapine

This guidance represents 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: Orally disintegrating tablet; oral

Recommended Studies: One study

1. Type of study: Steady-state
   Design: Two-way 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. Clozapine bioequivalence studies should not be conducted in healthy subjects.

Additional Comments: According to the randomization schedule, an equal number of patients should 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 should 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 may be continued on their maintenance dose of clozapine using an approved clozapine product as prescribed.

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, 150 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: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website, 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).