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Draft Guidance on Clozapine

February 2022

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In August 2017, FDA issued a finalized product-specific guidance for industry on generic clozapine. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Clozapine

Dosage Form; Route: Tablet, orally disintegrating; oral

Recommended Study: One study

1. Type of study: Steady-state
Design: Two-treatment, two-period crossover in vivo
Strength: 100 mg
Subjects: Schizophrenia patients who have been receiving a stable dose of clozapine at the same multiples of 100 mg every 12 hours for at least three months
Additional comments:
 1. The orally disintegrating tablet should be placed on the tongue, allowed to disintegrate, and swallowed without water.

2. Exclude patients if their smoking status or concomitant medications of known inhibitors or inducers of CYP3A4 or CYP1A2 is expected to change during the study.
3. Administer the same individualized dose for both the test and reference products for 10 days to each patient with no washout period between the two treatments.
4. Monitor absolute neutrophil count and blood pressure during the study.
5. Discontinue patients from the study if they require any dosage modification of clozapine treatment during the study.
6. Clozapine orally disintegrating tablets are approved under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

Analyte to measure: 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 strengths based on (i) acceptable bioequivalence study on the 100 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

Revision History: Recommended May 2015; Finalized August 2017; Revised February 2022

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