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Draft Guidance on Clozapine

February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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 December 2016, FDA issued a draft 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 We are now issuing revised draft guidance for industry that replaces the previously issued guidance.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: Suspension; oral

Recommended Study: One study

1. Type of study: Steady-state
   Design: Two-treatment, two-period crossover in vivo
   Strength: 50 mg/mL
   Subjects: Schizophrenia patients who have been on a stable once daily evening dose of an approved clozapine drug product (ideally oral suspension product). Patients should continue their established maintenance once daily evening dose throughout the study.

Additional comments:

1. 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.
2. Monitor absolute neutrophil count and blood pressure during the study.
3. Exclude patients with expected changes in smoking status or concomitant medications which are known to be inhibitors and/or inducers of CYP3A4 or CYP1A2.
4. Discontinue patients from the study if they require any dosage modification of clozapine treatment during the study.
5. Clozapine suspension is 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: Not applicable

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 the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional Information:

Device:

This product is a drug-device combination product. Refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a] An ANDA for a proposed generic drug-device combination product should include complete comparative analyses.

Revision History: Recommended December 2016; Revised February 2022

Unique Agency Identifier: PSG_203479

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents