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Draft Guidance on Ursodiol

March 2021

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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 July 2008, FDA issued a draft product-specific guidance for industry on generic ursodiol. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Ursodiol

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 500 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of ursodiol. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 500 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.
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Analytes to measure: Unconjugated ursodiol and total ursodiol (unconjugated plus glycine and taurine-conjugated) in plasma.

Measure baseline ursodiol concentrations at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. If the baseline concentrations are stable, consider a baseline correction for 24 hours rather than 48 hours. The mean of the pre-dose ursodiol concentrations should be used for the baseline correction. Subjects should continue to receive standard meals at regular intervals post-dose. For the fed study only, administer a standard breakfast to the subjects 30 minutes prior to the -48, -24 and 0 hour sample collection time points.

Bioequivalence based on (90% CI): Baseline-corrected (i) unconjugated ursodiol and (ii) total (conjugated and unconjugated) ursodiol.

Waiver request of in vivo testing: 250 mg based on (i) acceptable bioequivalence studies on the 500 mg strength, (ii) proportionally similar of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both 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 each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per Guidance for Industry on Tablet Scoring: *Nomenclature, Labeling, and Data for Evaluation*.

Revision History: Recommended July 2008; Revised March 2021

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