Contains Nonbinding Recommendations

Draft Guidance on Ursodiol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Ursodiol

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 500 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: Female subjects should be excluded from the studies if they are pregnant.

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2. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 500 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comment above.

Analytes to measure: Unconjugated Ursodiol and total Ursodiol (unconjugated plus glycine and taurine-conjugated) in plasma.

For both the fasting and the fed studies, please measure baseline ursodiol levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hours before dosing. For the fed study only, a standard breakfast should be administered to the subjects 30 minutes prior to the -48, -24 and 0 hour sample collection time points. If the baseline is stable, you may choose to do baseline correction for 24 hours rather than 48 hours. Subjects should continue to receive standard meals at regular intervals post-dose. The mean of the pre-dose ursodiol levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC.

Bioequivalence based on (90% CI): Baseline corrected and uncorrected (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 across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please 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 application.