

Draft Guidance on Cholic Acid

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Cholic Acid

Dosage Form; Route: Capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 250 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Females should not be pregnant or lactating, and, if applicable, should practice abstinence or contraception during the study.
2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 250 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Unconjugated cholic acid and total cholic acid (unconjugated cholic acid, glycocholic acid, and taurocholic acid) in plasma.

Since cholic acid is an endogenous substance, for both fasting and fed studies, the plasma concentrations of cholic acid should be corrected for baseline endogenous levels by subtracting the mean value of pre-dose levels at -48, -42, -36, -30, -24, -18, -12, -6, and 0 hour baseline time points from each subsequent cholic acid concentration obtained after dosing and used for all pharmacokinetic (PK) calculations. Any negative values obtained from baseline correction at time 0 hour should be designated as zero (0) and any subject with pre-dose concentrations (at time 0 hour) greater than 5% of their C_{max} should be excluded from the bioequivalence (BE) statistical analysis and the 90% confidence intervals (CIs) based on the remaining subjects. 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, measurement of baseline levels for 24 hours rather than 48 hours may be conducted. Subjects should continue to receive standard meals at regular intervals post-dose. Baseline concentrations should be determined for each dosing period and should be period specific. See appendix for additional information regarding endogenous compounds.

Bioequivalence based on (90% CI): Baseline corrected (i) unconjugated cholic acid and (ii) total cholic acid (unconjugated cholic acid, glycocholic acid, and taurocholic acid).

Waiver request of in vivo testing: In vivo bioequivalence testing may be waived for the 50 mg strength based on (i) acceptable bioequivalence studies on the 250 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 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.

Appendix:

Endogenous compounds are drugs that are already present in the body because the body produces them or they are present in the normal diet. Determining the amount of drug released from the dosage form and absorbed by each subject can be difficult because these compounds are identical to the drug that is administered. OGD recommends that applicants measure and approximate the baseline endogenous levels in blood (plasma) and subtract these levels from the total concentrations measured from each subject after the drug product is administered. In this way, applicants can achieve an estimate of BE of the products. Depending on whether the endogenous compound is naturally produced by the body or is present in the diet, the recommended approaches for determining BE differ as follows:

- When the body produces the compound, OGD recommends that applicants measure multiple baseline concentrations in the time-period before administration of the study drug and subtract the baseline in an appropriate manner consistent with the PK properties of the drug.
- In addition, when there is dietary intake of the compound, OGD recommends that applicants strictly control the intake both before and during the study. Subjects should be housed at a clinic before the study and served standardized meals containing an amount of the compound similar to that in the meals served on the PK sampling day.

For both of the approaches above, OGD recommends that applicants determine baseline concentrations for each dosing period that are period specific. If a baseline correction results in a negative plasma concentration value, the value should be set equal to 0 before calculating the baseline-corrected AUC. PK and statistical analysis should be performed on both uncorrected and corrected data. Determination of BE should be based on the baseline-corrected data.