

Draft Guidance on Alendronate Sodium; Cholecalciferol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Alendronate Sodium; Cholecalciferol

Form/Route: Tablets; Oral

Recommended studies: 1 Study

Type of study: Fasting

Design: Single-dose, two-way crossover *in-vivo*

Strength: 70 mg/5600 IU

Subjects: Healthy males and non-pregnant females, general population

Additional Comments: (1) A highly selective assay capable of low ng/mL limit of quantitation should be utilized. (2) Applicants may consider using a reference-scaled average bioequivalence approach for alendronate. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, please refer to the Draft Guidance on Progesterone Oral Capsules at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>. (3) To assist with achieving a stable plasma cholecalciferol baseline, subjects should receive a stable diet for a period preceding dosing and during plasma sample collection. Subjects should avoid all active vitamin D compounds and vitamin D-supplemented foods. In addition, subjects should avoid prolonged, direct sunlight for at least 10 days prior to- and during the study periods/washout.

Analytes to measure (in appropriate biological fluid): Alendronate and cholecalciferol in plasma

Bioequivalence based on (90% CI): Alendronate and cholecalciferol

Special Considerations: Because cholecalciferol (Vitamin D₃) is endogenously produced, post-dose plasma concentrations should be corrected for each subject per treatment period. Baseline plasma cholecalciferol concentrations should be determined from the average of at least four (4) samples collected between -24 and 0 hours (inclusive) prior to dosing.

For each treatment, test or reference, the mean of the endogenous plasma cholecalciferol concentrations from these four (or more) time points should be used for baseline adjustment. If baseline-adjusted concentrations are negative, concentrations should be set to zero (0.0). Statistical analysis should be performed on both baseline-adjusted and unadjusted pharmacokinetic parameters. BE should be established from the baseline-adjusted values and meet the standard 90% CI criteria for AUC_t, AUC_∞, and C_{max} pharmacokinetic criteria.

Waiver request of in-vivo testing: 70 mg/2800 IU based (i) acceptable bioequivalence studies on the 70 mg/5600 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling time: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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