Contains Nonbinding Recommendations

Draft Guidance on Alendronate Sodium and Cholecalciferol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 and 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 nonpregnant females, general population.
Additional Comments: 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.

Applicants may consider using a reference-scaled average bioequivalence approach for alendronate. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters total cumulative drug excreted in urine (Total Ae) and/or maximum urine excretion rate (Rmax) (i.e., within-subject variability $\geq$ 30%). For general information on this approach, please refer to Haidar et al. Bioequivalence Approaches for Highly Variable Drugs and Drug Products. *Pharm. Res.* ***25****:*237-241(2008).

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

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

The bioequivalence of alendronate should be based on urinary excretion data. The following pharmacokinetic parameters should be calculated:

Ae (amount of drug excreted during each collection interval)
Total Ae (0-48) (total amount of drug excreted over the entire period of sample collection)
Re (rate of drug excretion)
Rmax (maximum excretion rate) and
Tmax (time of the maximum excretion rate)

All parameters should be calculated using a noncompartmental model. The statistical analysis using ANOVA should be performed on Total Ae (0-48) and Rmax. The 90% confidence interval criteria should be applied to these parameters and should be within the limits of 80-125%.

The bioequivalence of cholecalciferol should be based on plasma levels using a validated method of analysis. Because cholecalciferol (Vitamin D3) is endogenously produced, post-dose plasma concentrations should be adjusted 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 adjusted. 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 AUCt, AUC∞, and Cmax pharmacokinetic criteria

Waiver request of in-vivo testing: 70 mg/2800 IU based on based on (i) acceptable bioequivalence studies on the 70 mg/5600 IU 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 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.