Contains Nonbinding Recommendations

Guidance on Doxercalciferol

This guidance represents 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: Doxercalciferol

Dosage Form: Route: Capsules; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two way crossover in-vivo
   Strength: 4 x 2.5 mcg (10 mcg dose)
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: None

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2. Type of Study: Fed
   Design: Single-dose, two way crossover in-vivo
   Strength: 4 x 2.5 mcg (10 mcg dose)
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: None

Analytes to measure (in appropriate biological fluid): Doxercalciferol (1α (OH) D_2) and its metabolite 1α, 25-$(OH)_2D_2$ in plasma. The assays should be sufficiently specific to distinguish both endogenous and exogenous Vitamin D-related compounds from the parent and metabolite in the biological matrix.

For 1α, 25-$(OH)_2D_2$, please submit individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

The plasma concentrations of doxercalciferol should be corrected for baseline endogenous levels by subtracting the mean value of four pre-dose levels at -24, -16, -8 and 0 hour baseline time points from each subsequent doxercalciferol concentration obtained after dosing and used for all pharmacokinetic calculations. Any negative values obtained from baseline correction at time 0 hour, should be designated as zero (0) and any subject with pre-dose concentration more than 5% of their C_{max} should be excluded from BE statistical analysis and the 90% confidence intervals based on the remaining subjects.

Bioequivalence based on (90% CI): Doxercalciferol

If the parent drug levels are too low to allow reliable analytical measurement in plasma, the data of the metabolite, 1α, 25-$(OH)_2D_2$, should be subjected to the confidence interval approach.

Waiver request of in-vivo testing: 0.5 mcg and 1 mcg based on (i) acceptable bioequivalence studies on the 2.5 mcg strength, (ii) acceptable dissolution testing of all strengths and (iii) proportional similarity in 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 web site, 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 (ANDA).