Contains Nonbinding Recommendations

Draft Guidance on Doxercalciferol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsules/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two way crossover *in-vivo*
   Strength: 4 x 2.5 mcg (10 mcg dose)
   Subjects: Normal healthy males and females, general population
   Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.

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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: Normal healthy males and females, general population
   Additional Comments: Please see comment above.

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 Cmax 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 based on (i) acceptable bioequivalence studies on the 2.5 mcg strength, (ii) acceptable dissolution testing of all strengths and (iii) proportionally similar in the formulations across 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.