Contains Nonbinding Recommendations

Draft Guidance on Sapropterin Dihydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in vivo*
   Strength: 100 mg tablet (Dose 10 mg/kg)
   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. Dissolving the tablets in 120 to 240 mL of water and taking the solution within 15 min are recommended. Because Sapropterin is supplied as 100 mg tablets, the dose for each subject should be calculated by multiplying the subject's weight by 10 mg/kg and then rounding up to the next 100 mg dose. For example, the weight of a 70.5 kg subject would be multiplied by 10 mg/kg, resulting in 705 mg and after rounding up this subject would be assigned a dose of 800 mg, or 8 tablets. Actual total dose should be included in the Analysis of Variance (ANOVA) statistical model. Dose normalization is not advised.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in vivo*
   Strength: 100 mg tablet (Dose 10 mg/kg)
   Subjects: Normal healthy males and females, general population.
   Additional Comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Sapropterin (Tetrahydrobiopterin, BH4)

Please provide baseline adjustment for endogenous sapropterin in the analysis. Please measure baseline sapropterin levels at -1, -0.5 and 0 hours. The mean of the pre-dose sapropterin levels should be used for the baseline adjustment of the post-dose levels. Any negative values obtained from baseline adjustment should be designated as zero (0) and any subject with baseline-adjusted pre-dose concentrations (at time 0 hour) greater than 5% of their Cmax should be excluded from the bioequivalence statistical analysis and the 90% confidence interval is calculated based on the remaining subjects.

Bioequivalence based on (90% CI): Sapropterin (Tetrahydrobiopterin, BH4)

Waiver request of in-vivo testing: Not Applicable

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.