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Draft Guidance on Sapropterin Dihydrochloride

October 2024

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Active Ingredient: Sapropterin dihydrochloride

Dosage Form: Tablet

Route: Oral

Strength: 100 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 100 mg (Dose 10 mg/kg)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Females 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.

Analytes to measure: Sapropterin (Tetrahydrobiopterin, BH4)

Provide baseline adjustment for endogenous sapropterin in the analysis. 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 C_{max} 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: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution. Conduct comparative dissolution testing on 12 dosage units for each of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended September 2008; Revised September 2012, October 2024

Unique Agency Identifier: PSG_022181

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*