Contains Nonbinding Recommendations

Draft Guidance on Doxylamine Succinate; Pyridoxine Hydrochloride

Active ingredient: Doxylamine Succinate; Pyridoxine Hydrochloride

Form/Route: Delayed Release Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 10 mg /10 mg (Recommended dose: 2 x 10 mg/10 mg tablets)
   Subjects: Healthy nonpregnant females
   Additional Comments: Study subjects should avoid consuming foods/beverages with high vitamin B6 contents or vitamin B6 supplements for appropriate periods of time before and during the study. Applicants may consider using a reference-scaled average bioequivalence approach for the component of pyridoxine. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$30%). Please refer to the Progesterone Capsule Draft Guidance for additional information regarding highly variable drugs.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 10 mg /10 mg (Recommended dose: 2 x 10 mg/10 mg tablets)
   Subjects: Healthy nonpregnant females
   Additional Comments: See additional comments above.

Analytes to measure (in appropriate biological fluid): Doxylamine, pyridoxine and active metabolites of pyridoxine, pyridoxal 5'-phosphate and pyridoxal in plasma

Bioequivalence based on (90% CI): Doxylamine and pyridoxine

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

The plasma levels of pyridoxal and pyridoxal 5'-phosphate should be corrected with their baseline levels. Both baseline-corrected and uncorrected data should be submitted for review.

Since pyridoxal 5'-phosphate has a relatively long half-life, to avoid carryover, adequate washout period should be used for both BE studies.

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.accessdata.fda.gov/scripts/cder/dissolution/. 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.