

## Draft Guidance on Doxylamine Succinate; Pyridoxine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:** Doxylamine succinate; Pyridoxine hydrochloride

**Dosage Form; Route:** Extended release tablet; Oral

**Recommended Studies:** Two studies

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 20 mg /20 mg  
Subjects: Non-lactating, non-pregnant females, general population  
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, provide evidence from the study of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability >30%). Refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

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2. Type of study: Fed  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 20 mg /20 mg  
Subjects: Non-lactating, non-pregnant females, general population  
Additional comments: See comments in Study 1.

**Analytes to measure:** Doxylamine, pyridoxine and active metabolites of pyridoxine, pyridoxal 5'-phosphate and pyridoxal in plasma

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

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, 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 concentrations of pyridoxal and pyridoxal 5'-phosphate should be corrected with their baseline concentrations. Both baseline-corrected and uncorrected data should be submitted

for review. Refer to the Guidance on Ergocalciferol Capsule for additional information regarding endogenous compounds.

**Additional strengths:** Not applicable

**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).

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary.

Both test and reference listed drug products should be tested accordingly and data should be provided on individual unit, means, range and %CV.