This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Tiopronin

Dosage Form: Route: Delayed release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period, crossover in vivo
   Strength: 300 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Tiopronin has a long terminal elimination half-life (>24 hours). Ensure that there are adequate washout periods between treatments in the crossover studies to avoid the carry-over from the first period. Alternatively, consider using a parallel study design for the drug with a long half-life.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period, crossover in vivo
   Strength: 300 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analyte to measure (in appropriate biological fluid): Tiopronin in plasma

Bioequivalence based on (90% CI): Tiopronin

Additional strength: Bioequivalence of the 100 mg strength to the corresponding reference product strength may be demonstrated based on principles laid out in the FDA guidance for industry, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.

Dissolution test method and sampling times: For modified-release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA’s database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/), provided adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed,
FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Alcohol dose dumping studies:**

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 1 (basket) @100 rpm, with or without alcohol

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 5: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

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