

Draft Guidance on Topiramate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Capsule (extended-release); oral

Recommended Studies: Three studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 200 mg
Subjects: Normal healthy males, general population
Additional comments: 1. Due to the risk of teratogenicity of topiramate, the study should be conducted in healthy male volunteers. 2. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after topiramate extended-release capsule administration. 3. Topiramate extended-release capsules should be swallowed whole, not chewed or crushed.

2. Type of study: Sprinkle bioequivalence (BE) study
Design: Single-dose, two-way crossover in vivo
Strength: 200 mg
Subjects: Normal healthy males, general population
Additional comments: 1. Due to the risk of teratogenicity of topiramate, the study should be conducted in healthy male volunteers. 2. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after topiramate extended-release capsule administration. 3. Topiramate extended-release capsules should be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (i.e., a teaspoon) of soft food (e.g., apple sauce). This drug/food mixture should be swallowed immediately, not chewed or crushed.

3. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 200 mg
Subjects: Normal healthy males, general population
Additional comments: Same as Study 1 above

Analytes to measure (in appropriate biological fluid): Topiramate

Bioequivalence based on (90% CI): Topiramate

Approval of other strengths: 25 mg, 50 mg, 100 mg, and 150 mg based on (i) acceptable BE studies on the 200 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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 U.S. Pharmacopoeia (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. Increase agitation speeds if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, 0.1 N HCl, USP Apparatus I (basket) @ 100 rpm, with and without the alcohol (see below):

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

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

Test 3: 12 units analyzed by substituting Alcohol USP for 20% (v/v) of the test medium, with data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting Alcohol USP for 40% (v/v) of the test medium, with data collection every 15 minutes for a total of 2 hours

Both test and reference Listed Drug products must be tested accordingly, and data must be provided on individual unit, means, range, and %CV for all strengths.