Contains Nonbinding Recommendations

Draft Guidance on Phentermine Hydrochloride; Topiramate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule, Extended Release/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 15 mg base; 92 mg
   Subjects: Healthy males, general population.
   Additional comments: Due to the risk of teratogenicity of topiramate, the study should be conducted in healthy male volunteers. The Reference Listed Drug (RLD) was approved with a Risk Evaluation and Mitigation Strategy (REMS), which restricts its use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 15 mg base; 92 mg
   Subjects: Healthy males, general population.
   Additional comments: Please see comment above. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Phentermine and topiramate in plasma

Bioequivalence based on (90% CI): Phentermine and topiramate

Waiver request of in vivo testing: EQ 3.75 mg/23 mg, EQ 7.5 mg base/46 mg and EQ 11.25 mg base/69 mg based on (i) acceptable bioequivalence studies on the EQ 15 mg base/92 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

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. 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. Please 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 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: 750 mL, de-aerated de-ionized water, USP Apparatus 1 (basket) @100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with de-aerated de-ionized water), 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 3: 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 4: 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 RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.