Contains Nonbinding Recommendations

Draft Guidance on Topiramate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet /Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 25 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: Due to safety concerns, studies should be conducted on the 25 mg strength.

   Animal studies with topiramate have demonstrated selective developmental toxicity, including teratogenicity. Although no studies have been conducted in pregnant women taking topiramate, in post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. Therefore the following precautions are recommended for the bioequivalence study:
   - Pregnant women should be excluded from the study, and a negative pregnancy test should be required within 24 hours before dosing for all women of childbearing potential.
   - Women of childbearing potential should be enrolled only if using an effective method of contraception.
   - Written informed consent must include the finding of birth defects in animal studies and the unknown risk to a human fetus if exposed to this drug.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 25 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Topiramate in plasma.

Bioequivalence based on (90% CI): Topiramate

Waiver request of in-vivo testing: 50 mg, 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 25 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:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. 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.