Contains Nonbinding Recommendations

Draft Guidance on Oxcarbazepine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover in vivo
   Strength: 600 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments:
   a. As oxcarbazepine is likely to be a teratogen, sexually active women of reproductive age should be using highly effective contraception (for example, sterilization, intrauterine devices, combination birth control pills, or hormonal implants) and should have a negative pregnancy test immediately before receiving each dose of oxcarbazepine. Counseling about teratogenicity should be part of the consent process. Alternatively, women could be excluded from the studies.
   b. Because coadministration of oxcarbazepine substantially decreases exposure to estradiol and levonorgestrel, women who are relying on hormonal contraception (including hormonal implants or combination hormonal pills/patches/vaginal rings) may experience decreased effectiveness of their contraception during the menstrual cycle in which they are exposed to oxcarbazepine. This could result in unplanned pregnancy. Women should be counseled to use a barrier method, such as condoms or diaphragm, in addition to their usual hormonal method, for three weeks following BE study.

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2. Type of study: Fed
   Design: Single-dose, two-way, crossover in vivo
   Strength: 600 mg
   Subjects: Healthy males and non-pregnant females, general population.
   Additional Comments: Please see above. Please also refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Oxcarbazepine and its active metabolite, 10-monohydroxy derivative (MHD) in plasma using an achiral assay.

Bioequivalence based on (90% CI): Oxcarbazepine

Waiver request of in vivo testing: 150 mg and 300 mg based on (i) acceptable bioequivalence studies on the 600 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please refer to Mirtazapine Tablet Draft Guidance for additional information regarding waiver 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 with justification, if necessary. To provide assurance against premature release of drug (dose dumping) from the formulation, please include early sampling times of at least 0.25, 0.5, 0.75, 1, 1.5, 2 and 4 and continue every 2 hours until at least 80% of the drug is released.

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, 0.1N HCl, USP apparatus 2 (paddle) @75 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 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.