Contains Nonbinding Recommendations

Draft Guidance on Ropinirole Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 2 mg
   Subjects: Males and nonpregnant females, general population
   Additional comments: Due to safety concerns, bioequivalence studies should be conducted using the 2 mg strength.

   The subjects should remain in a comfortable recumbent position for up to 8 hours after dosing and remain under medical surveillance for up to 12 hours after dosing. Before they are allowed to ambulate, they should sit up with legs in a dependent position for one minute prior to standing up. While standing immobile, they should be closely observed for blood pressure changes and/or orthostatic symptoms, including nausea, dizziness, or faintness for at least three minutes.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 2 mg
   Subjects: Males and nonpregnant females, general population
   Additional comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Ropinirole in plasma

Bioequivalence based on (90% CI): Ropinirole

Waiver request of in vivo testing: 4 mg, 6 mg, 8 mg and 12 mg based on (i) acceptable bioequivalence studies on the 2 mg strength, (ii) acceptable in vitro dissolution testing across all strengths, and (iii) proportional similarity across all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, 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 USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three different pH dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer) and water 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 concerns of dose dumping from this drug product when taken with alcohol, the Agency currently requests that additional in vitro dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 500 mL, 0.1 N HCl, apparatus II (Paddle) @ 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 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.

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution plots.