Contains Nonbinding Recommendations

Draft Guidance on Hydromorphone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet, Extended Release/Oral

Recommended study: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 32 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments:
   1) A naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg – 100 mg of naltrexone at the following times: (a) 12 hours prior to dosing; (b) at the time of study drug dosing; and (c) 12 hours after the last dose of study drug. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose and regimen of narcotic antagonist.
   2) Hydromorphone Hydrochloride (HCl) oral extended release (ER) tablet is under a Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the risks of accidental overdose, misuse and abuse and to inform patients of the serious risks associated with the Reference Listed Drug (RLD). All pertinent elements of the REMS must be incorporated into the bioequivalence study protocols and informed consents.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 32 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: See comments above. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

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

Bioequivalence based on (90% CI): Hydromorphone

Waiver request of in vivo testing: 8 mg, 12 mg, and 16 mg based on (i) acceptable bioequivalence studies on the 32 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 concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 2 (paddle) @ 50 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.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.