Contains Nonbinding Recommendations

Draft Guidance on Oxymorphone Hydrochloride

Active ingredient: Oxymorphone Hydrochloride

Form/Route: Extended Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 40 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments: Please use a narcotic antagonist such as naltrexone if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 40 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Oxymorphone and its metabolite, 6-OH-oxymorphone in plasma.

Bioequivalence based on (90% CI): Oxymorphone.

For 6-OH-oxymorphone, please submit individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in-vivo testing: 5 mg, 10 mg, and 20 mg based on (i) acceptable bioequivalence studies of the 40 mg strength, (ii) proportionally similar 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.

For modified release products, dissolution profiles 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 phosphate buffer, 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. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 75 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.