Contains Nonbinding Recommendations

Draft Guidance on Oxycodone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended-release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 36 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: A naltrexone blockade should be used to reduce 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 of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Consult with 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: 36 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See the comments above.

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3. Type of study: Fasting sprinkle-in-applesauce
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 36 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Administer the dose after sprinkling the entire contents of the capsule on a tablespoon of applesauce in accordance with the approved label of the RLD. Otherwise, the study should be conducted in the fasting state as described above. See the comments above regarding naltrexone blockade.

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

Bioequivalence based on (90% CI): Oxycodone

Waiver request of in vivo testing: 9 mg, 13.5 mg, 18 mg and 27 mg based on (i) acceptable bioequivalence studies on the 36 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Evaluating the abuse-deterrence: Since the FDA has determined that the reference listed drug for oxycodone extended-release capsules has abuse-deterrent properties (as described in section 9.2 of the approved Full Prescribing Information), the sponsor of a proposed generic version of the reference listed drug should refer to the guidance, "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products for Industry," regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the reference listed drug with respect to all potential routes of abuse.

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 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.

Due to concerns of dose dumping from this drug product when taken with alcohol, 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, USP apparatus 1 (basket) @100 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.

Product-specific testing conditions for in vitro feeding tube studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) or gastric (G) tube. Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution study, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Draft Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: NG tube (8 French), G tube (12 French)

Testing strengths: 36 mg

Dispersion medium: Disperse the capsule contents in 15 mL of water, milk and liquid nutritional supplement followed by flushing two more times, each with 10 mL of the same vehicle