Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Naloxone Hydrochloride; Oxycodone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two bioequivalence studies (1–2) and one in vivo abuse deterrence study (3)

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg; 40 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Incorporate naltrexone to block the pharmacodynamic effects of the opioid. Administer the opioid antagonist well in advance of opioid 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.

   Oxycodone hydrochloride; naloxone hydrochloride ER tablet is approved with a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg; 40 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments in Study 1.

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3. Type of study: Fasting, comparative nasal pharmacokinetic study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, for tier 2 evaluation of abuse by insufflation as applicable
   Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 20 mg; 40 mg
Subjects: Non-dependent recreational opioid users, general population[1]
Additional comments: See comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.[2] Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, oxycodone and naloxone content, and particle size distribution of physically manipulated test and reference drug products used in the comparative nasal pharmacokinetic study using validated analytical procedures. For both oxycodone and naloxone, determine relevant pharmacokinetic parameters including maximum concentration (Cmax), area-under-the-curve (AUC0-t, and AUC0-∞), and time to maximum concentration (Tmax). For oxycodone, applicants should submit partial AUCs (e.g., AUC0-3 hours and AUC0-4 hours) as supporting data.

Analytes to measure: Oxycodone and naloxone in plasma

Bioequivalence based on (90% CI): Oxycodone

Abuse deterrence based on: Upper 95% confidence bound for oxycodone; lower 95% confidence bound for naloxone (or naloxone-3β-glucuronide)

For the in vivo abuse deterrence study if naloxone can be reliably measured, the lower 95% confidence bound should be obtained for naloxone. If naloxone cannot be reliably measured, the lower 95% confidence bound should be obtained for naloxone-3β-glucuronide.

Additional strengths: Bioequivalence of the 20 mg;10 mg, and 10 mg;5 mg strengths to the corresponding reference product strengths may be demonstrated based on principles described in the FDA guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*

Abuse deterrence evaluation: Since the FDA has determined that the reference product for oxycodone hydrochloride and naloxone hydrochloride extended release tablet has properties that are expected to deter abuse (as described in Section 9.2 of the approved Full Prescribing Information), refer to the guidance, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the reference product with respect to all potential routes of abuse. Consistent with the guidance, the potential applicants should consider, among other things, the following:

[1] This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes.
[2] For criteria on evaluating substance dependence, refer to, for example, the latest version of *Diagnostic and Statistical Manual of Mental Disorders,* Arlington, VA, American Psychiatric Association.

(a) Conduct all in vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths;
(b) Ensure that the formulation components containing oxycodone hydrochloride and naloxone hydrochloride are not physically distinguishable (i.e., color, size, shape) to allow physical separation;
(c) Specify and justify the total number of tablets used in a manipulation run (e.g., milling).
(d) Determine the drug content in manipulated drug products (e.g. cut, grated or milled) and quantify the drug loss in samples prior to evaluating extractability.

Dissolution test method and sampling times: For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database, http://www.accessdata.fda.gov/scripts/cder/dissolution/, provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.
In addition to the method above, dissolution profiles on 12 dosage units for each strength of test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5, 6.8 buffer) should be submitted in the application. Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. 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.

Alcohol dose dumping studies: Due to concerns of dose dumping of oxycodone hydrochloride and naloxone hydrochloride from this product when taken with alcohol, conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 1 (basket) at 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

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.