Contains Nonbinding Recommendations

Draft Guidance on Hydrocodone Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1–2) and two in vivo comparative pharmacokinetic (PK) studies for abuse deterrence assessment (3–4)

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Naltrexone or other opioid antagonist should be incorporated to block the pharmacodynamic (PD) effects of the opioid. The opioid antagonist should be administered 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.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 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 oral PK study of chewed drug products
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products' ability of deterring chewing should be identified. Determine relevant PK parameters including maximum concentration (C_{max}), area-under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$) as supportive data.

4. Type of study: Fasting, comparative nasal PK 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: 60 mg
   Subjects: Non-dependent recreational opioid users, general population[1]
   Additional Comments: See all 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] Also see comments on PK parameters in Study 3. Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated test and reference drug products used in the nasal PK study using validated analytical procedures.

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

Bioequivalence based on (90% CI): Hydrocodone
Abuse deterrence based on (upper 95% confidence bound): Hydrocodone

Waiver request of in-vivo testing: 30 mg, 40 mg, 80 mg, 100 mg and 120 mg based on (i) acceptable bioequivalence studies on the 20 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Abuse Deterrence Evaluation: Since the FDA has determined that the reference listed drug (RLD) for hydrocodone bitartrate extended-release tablet (NDA 206627) has properties that are expected to deter abuse (as described in Section 9.2 of the approved Full Prescribing Information), you should 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 RLD with respect to all potential routes of abuse. Consistent with the guidance, the potential abbreviated new drug application (ANDA) applicants should consider, among other things, the following:

a) Conducting 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.

[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.

b) Conducting all in vitro abuse deterrence studies comparing test and reference products using an intermediate manipulation method (e.g., cutting, grating), in addition to "intact and most effectively physically manipulated drug products" as described in the general guidance.
c) Specifying and justifying the total number of tablet units used in a manipulation run (e.g., milling).
d) Determining the drug content in manipulated drug products (e.g., cut, grated, or milled) and quantifying the drug loss in samples prior to evaluating extractability.

Dissolution test method and sampling times:
The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the 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. 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 a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus I (basket) @100 rpm, with or without alcohol;

Test 1: 12 units tested per 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.