Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Levorphanol Tartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two options: Biopharmaceutics Classification System (BCS) or in vivo studies

I. **BCS Class 1-based biowaiver option**:

A waiver request of in vivo testing for this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate–Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System* is submitted in the application. Applicants may use information contained in the approved labeling of the reference product. Peer-reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request will be made upon assessing the data submitted in the application.

II. **In vivo bioequivalence study option:**

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 3 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: 1) Naltrexone or other opioid antagonist should be incorporated to block the pharmacodynamic 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: 12 hours prior to dosing; at the time of study drug dosing; and 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. 2) Levorphanol tartrate tablet is approved under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 3 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above

Analyte to measure: Levorphanol in plasma

Bioequivalence based on (90% CI): Levorphanol

Waiver request of in vivo testing: 1 mg and 2 mg based on (i) acceptable bioequivalence studies on the 3 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

If any strength of the drug product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per Guidance for Industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.