

Draft Guidance on Buprenorphine Hydrochloride; Naloxone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Sublingual tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 11.4 mg base/EQ 2.9 mg base
Subjects: Healthy males and non-pregnant, non-breastfeeding females, general population, 18 to 55 years of age (inclusive), with a minimum weight of 59 kg (129.8 lbs)
Additional Comments:
 - a) A naltrexone blockade should be used to minimize the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing, in order to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg to 100 mg of naltrexone tablets at the following times 12 hours and 0.5 hours pre-dose; and 50 mg at 12 hours and 24 hours post-dose. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of opioid antagonist.
 - b) Exclude subjects who have received any opioid within 14 days of dosing.
 - c) Tablet should be placed under the tongue until completely dissolved; tablet should not be moved after placement. Advise subjects not to cut, crush, break, chew or swallow the tablet.
 - d) The study design (e.g., inclusion/ exclusion criteria), procedures (e.g., safety monitoring), and concomitant medications (drug interactions) should address all of the elements related to patient safety specified in the RLD label.
 - e) A clear plan for continuous respiratory monitoring from the time of dosing past the time of expected peak effect of the drug (i.e., at least 3 hours after dosing) should be included. Standard operating procedures (SOPs) should be in place for assessing and treating ventilatory depression, and personnel qualified to treat ventilatory emergencies should be immediately available.
 - f) Buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet is under a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use (ETASU) (1) to mitigate the risks of accidental overdose misuse and abuse and (2) to inform patients of the serious risks associated with this drug product. All pertinent elements of this REMS and of the warnings in the approved labeling for buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet must be incorporated into the protocol and informed consent in the bioequivalence study.

Analytes to measure (in appropriate biological fluid): Buprenorphine and its active metabolite, norbuprenorphine, in plasma. For naloxone, measure unconjugated and total naloxone in plasma.

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Buprenorphine and naloxone

Waiver request of in vivo testing: EQ 0.7 mg base/EQ 0.18 mg base, EQ 1.4 mg base/EQ 0.36 mg base, EQ 2.9 mg base/EQ 0.71 mg base, EQ 5.7 mg base/EQ 1.4 mg base and EQ 8.6 mg base/EQ 2.1 mg base strengths based on (i) acceptable bioequivalence study on the EQ 11.4 mg base/EQ 2.9 mg base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).