Contains Nonbinding Recommendations

Draft Guidance on Buprenorphine Hydrochloride; Naloxone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Studies: One study

1. Type of study: Fasting

   Design: Single-dose, two-treatment, two-period crossover in vivo

   Strength: EQ 12 mg base/EQ 3 mg base

   Subjects: Healthy males and non-pregnant, non-lactating females, general population, aged 18 to 50 years

   Additional comments:

   A. Film should be placed under the tongue until they are completely dissolved; film should not be moved after placement. Advise subjects not to chew, swallow or cut the film.
   B. Exclude subjects who have received any opioid within 14 days of dosing.
   C. An opioid antagonist, such as Naltrexone Hydrochloride Oral Tablet, 50 mg, should be used to minimize opioid-related adverse events. The opioid antagonist should be administered well in advance of dosing, in order to achieve adequate blockade of opioid receptors. Please consult with a physician who is an expert in the administration of opioids for the appropriate dose and dosing regimen of an opioid antagonist for a single dose of buprenorphine hydrochloride and naloxone hydrochloride sublingual film EQ 12 mg base/EQ 3 mg base administered to a healthy volunteer who had not received any opioid within 14 days of dosing.
   D. 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.
   E. Buprenorphine Hydrochloride and Naloxone Hydrochloride Sublingual Film 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) 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 film must be

incorporated into the protocol and informed consent in the bioequivalence study.

F. The bioequivalence study be performed using either the sublingual or buccal route of administration. The same one route should be used for all subjects in both periods.

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

Please 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 2 mg base/EQ 0.5 mg base, EQ 4 mg base/EQ 1 mg base and EQ 8 mg base/EQ 2 mg base strengths based on (i) acceptable bioequivalence study on the EQ 12 mg base/EQ 3 mg base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please 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 web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please 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).

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