

## Draft Guidance on Buprenorphine Hydrochloride; Naloxone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Buprenorphine HCl; Naloxone HCl

**Dosage Form; Route:** Film; buccal

**Recommended Studies:** One study

1. Type of study: Fasting  
Design: Single-dose, two-way crossover, in vivo  
Strength: 6.3 mg; 1 mg Buprenorphine (base); Naloxone (base)  
Subjects: Healthy males and nonpregnant females, general population, aged 18 to 50 years

Additional comments:

- A. Film should be placed on the buccal area until completely dissolved; film should not be moved after placement. Subjects should not 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, may 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. 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 and naloxone buccal film 6.3 mg; 1 mg administered to a healthy volunteer who has 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 and naloxone buccal film is under a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use (ETASU) to (1) 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 and naloxone buccal film must be incorporated into the protocol and informed consent in the bioequivalence (BE) study.

**Analytes to measure (in appropriate biological fluid):** Buprenorphine and its active metabolite, nor-buprenorphine, 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 Cmax.

**Bioequivalence based on (90% CI):** Buprenorphine and Naloxone

**Waiver request of in vivo testing:** Buprenorphine (base); Naloxone (base) 4.2 mg; 0.7 mg and 2.1 mg; 0.3 mg buccal films based on (i) acceptable BE study on the 6.3 mg; 1 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

**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).