

Draft Guidance on Naltrexone Hydrochloride; Bupropion Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended-release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting

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

Strength: Naltrexone hydrochloride/bupropion hydrochloride 8 mg/90 mg × 2 tablets (16 mg/180 mg)

Subjects: Healthy males and nonpregnant females, general population

Additional comments: Per the currently approved reference listed drug (RLD) labeling, exclude following subjects who have:

- 1) A seizure disorder or a history of seizures
- 2) A current or prior diagnosis of anorexia nervosa or bulimia
- 3) An abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
- 4) A history of head trauma or prior seizure, severe stroke, arteriovenous malformation, central nervous system tumor or infection, or metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia)
- 5) An excessive use of alcohol or sedatives, addiction to cocaine or stimulants, or withdrawal from sedatives
- 6) Diabetes treated with insulin and/or oral diabetic medications (sulfonylureas and meglitinides) that may cause hypoglycemia
- 7) Concomitant administration of monoamine oxidase inhibitors (MAOI); at least 14 days should elapse between discontinuation of MAOI and initiation of the study
- 8) Concomitant administration of medications that may lower the seizure threshold, including antipsychotics, tricyclic antidepressants, theophylline, and systemic steroids

2. Type of study: Fed

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

Strength: Naltrexone hydrochloride/bupropion hydrochloride 8 mg/90 mg × 2 tablets (16 mg/180 mg)

Subjects: Healthy males and nonpregnant females, general population

Additional comments: Same as comments above

Analytes to measure (in appropriate biological fluid): Naltrexone and its active metabolite, 6-beta-naltrexol, in plasma; bupropion and its active metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, 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): Naltrexone and bupropion

Waiver request of in vivo testing: Not applicable

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/>. Conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of the test and reference products generated using U.S. Pharmacopeia (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 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. Specifications will be determined upon review of the data submitted in the application.

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 1 (basket) @75 rpm, with or without alcohol

Test 1: 12 units tested according to 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.