

Draft Guidance on Bupropion Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Bupropion Hydrochloride

Form/Route: Extended-Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 450 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional comments: Exclude subjects per the currently approved Reference Listed Drug (RLD) labeling, e.g., prior seizure, seizure disorder or epilepsy, central nervous system tumor, severe hepatic cirrhosis, history of head trauma, current depression, current or prior diagnosis of bulimia or anorexia nervosa, taken a monoamine oxidase (MAO) inhibitor within 14 days prior to dosing, allergic to any active or inactive ingredient in the study medications or undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines). Prohibit the concomitant administration of drug products per the currently approved RLD labeling, e.g., any MAO inhibitor, antipsychotic, antidepressant, theophylline, systemic steroid and any other drug products containing bupropion hydrochloride or bupropion hydrobromide.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 450 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional comments: See above Additional comments for Study 1. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Bupropion and its active metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, in plasma.

Please submit the metabolites data as supportive evidence of comparable therapeutic outcome. For the metabolites, 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): Bupropion

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. 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 application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using 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 have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please 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 concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing 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), and data collected every 15 minutes for a total of 2 hours

Test 2: 12 units tested 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 tested 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 tested 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 on all strengths.