

Draft Guidance on Bupropion Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Tablet, Extended-Release; Oral

Recommended studies: 2 studies

1. Type of study: Fasting

Design: Single-dose, two-way crossover in-vivo

Strength: 200 mg

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments:

2. Type of study: Fed

Design: Single-dose, two-way crossover in-vivo

Strength: 200 mg

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.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 metabolite 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: 100 mg and 150 mg based on (i) acceptable bioequivalence studies on the 200 mg 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 Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.

Please note that Zyban[®] Tablets, 150 mg, and Wellbutrin[®] SR Tablets, 50 mg, 100 mg, 150 mg and 200 mg are the subject of two separate reference products. Two separate applications must

be submitted comparing to the appropriate reference products. An applicant may request a waiver of in vivo bioequivalence testing for the 150 mg strength using Zyban[®] Tablets as RLD provided that it (1) submits an ANDA containing acceptable in vivo studies on the 200 mg strength using Wellbutrin[®] SR Tablets as RLD; (2) cross-references the ANDA for the 150 mg strength using Wellbutrin[®] SR Tablets as RLD; and (3) meets the criteria of 21 CFR §320.24(b)(6). Please refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA* located at: <http://www.fda.gov/cder/guidance>.

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 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 2 (paddle) @ 50 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 on both strengths.