

Draft Guidance on Bupropion Hydrochloride; Naltrexone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients: Bupropion hydrochloride; Naltrexone 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: 90 mg; 8 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 90 mg; 8 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: None

Analytes to measure: Bupropion and its active metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, in plasma; naltrexone and its active metabolite, 6-beta-naltrexol, in plasma

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 area under the curve and maximum concentration.

Bioequivalence based on (90% CI): Bupropion and naltrexone

Additional strengths: Not applicable

Dissolution test method and sampling times:

For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph or in the FDA's database,

<http://www.accessdata.fda.gov/scripts/cder/dissolution/>), provided that applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer). 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.

Due to concerns of dose dumping of drugs from this product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP Apparatus 1 (basket) at 75 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1 N 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

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.