

Draft Guidance on Carbidopa; Levodopa

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule, extended-release; oral

Recommended Studies: Three studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 61.25 mg/245 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 61.25 mg/245 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: None

3. Type of study: Fasting sprinkle-in-applesauce
Design: Single-dose, two-way crossover in vivo
Strength: 61.25 mg/245 mg
Subjects: Healthy males and nonpregnant females, general population
Additional comments: Carefully open the capsule, sprinkle the entire contents on a small amount of applesauce (1 to 2 tablespoons), and consume. The contents of the capsule should not be crushed or chewed.

Analytes to measure (in appropriate biological fluid): Carbidopa and levodopa in plasma

Bioequivalence based on (90% CI): Carbidopa and levodopa

Waiver request of in vivo testing: 23.75 mg/95 mg, 36.25 mg/145 mg, and 48.75 mg/195 mg strengths, based on (i) acceptable bioequivalence studies on the 61.25 mg/245 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, (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 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 each of all strengths 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, applicants should submit in the application dissolution profiles on 12 dosage units each of 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). 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 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 (v/v) 5% Alcohol USP for test medium, with data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting (v/v) 20% Alcohol USP for test medium, with data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting (v/v) 40% Alcohol USP for test medium, with 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.