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Draft Guidance on Carbidopa; Entacapone; Levodopa

October 2024

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Active Ingredients: Carbidopa; Entacapone; Levodopa

Dosage Form: Tablet

Route: Oral

Strengths: 12.5 mg; 200 mg; 50 mg, 18.75 mg; 200 mg; 75 mg, 25 mg; 200 mg; 100 mg, 31.25 mg; 200 mg; 125 mg, 37.5 mg; 200 mg; 150 mg, 50 mg; 200 mg; 200 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 50 mg; 200 mg; 200 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference listed drug. For detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 12.5 mg; 200 mg; 50 mg
   Subjects: Healthy males and nonpregnant, non-lactating females
   Additional comments: See comments above.

Analytes to measure: Carbidopa, entacapone and levodopa in plasma

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

Waiver requests of in vivo testing: 18.75 mg; 200 mg; 75 mg, 25 mg; 200 mg; 100 mg, 31.25 mg; 200 mg; 125 mg, and 37.5 mg; 200 mg; 150 mg strengths, based on (i) acceptable bioequivalence studies on the 12.5 mg; 200 mg; 50 mg and 50 mg; 200 mg; 200 mg strengths, (ii) acceptable in vitro dissolution testing of all strengths, and (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 in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.