Contains Nonbinding Recommendations

Draft Guidance on Carbidopa; Levodopa

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Enteral suspension; jejunum via a percutaneous endoscopic gastrostomy (PEG) with the portable infusion pump through jejunal (PEG-J) or naso-jejunal (NJ) tube

Recommended Studies: One study

1. Type of study: Continuous infusion with the portable infusion pump through PEG-J or NJ tube
   Design: Steady state, two-way crossover *in vivo*
   Strength: 4.63 mg/mL and 20 mg/mL
   Subjects: Male and female patients with advanced Parkinson's disease with the established dosing regimen for Carbidopa-Levodopa Enteral Suspension (CLES).
   Additional Comments: a. The bioequivalence (BE) study should be conducted in patients with advanced Parkinson's disease undergoing indicated therapy, who have already been receiving a stable dose of CLES. After the study is completed, the patients should be continued on their established dosing regimens for CLES. b. The size of tube and function of infusion pump should follow the dosage and administration section of the reference listed drug (RLD) labeling. The drug formulation is a suspension of 5 mg/mL carbidopa monohydrate and 20 mg/mL levodopa in water. One medication cassette reservoir supplies up to 500 mg of carbidopa monohydrate and 2000 mg levodopa. The total daily dose should be administered as the mode of administration recommended in the RLD labeling, including the morning dose, the continuous maintenance dose, and the extra doses. Each period of the study should have the same dose and administration. If dosage changes are necessary between study periods then that patient should be excluded from the study.

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

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

In the evaluation of the steady-state BE study, the following Pharmacokinetic (PK) data should be submitted for carbidopa and levodopa: AUC_{0-16}, AUC_{0-t}, AUC_{0-24}, and C_{maxSS}. In addition, C_{avSS} (average concentration during 16 hrs. infusion), degree of fluctuation $[(Cmax-C_{min})/C_{avSS}]$, swing $[(C_{maxSS}-C_{minSS})/C_{minSS}]$, and Tmax should be reported.

Waiver request of in-vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units (Single-use cassette) each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In Vitro Comparative Compatibility Studies:

The approved labeling for the reference product states that the product should be administered into the jejunum with portable infusion pump through a PEG-J or NJ tube. The detailed recommended tubing sets for PEG-J and NJ administration are listed in the approved labeling for the reference product. Conduct the following in vitro comparative compatibility testing using French size 8.5 for J tube and size 10 for NJ tube to compare the performance of the test product to that of the reference product to support PEG-J or NJ tube administration. The applicant should consider the material of various PEG-J and NJ tubes that may be used for product administration, and justify why the equivalence testing conducted below is sufficient for risk evaluation. Justification of testing conditions may be made on the basis of recovery studies (for testing procedure, see #2 below). Studies should be performed demonstrating the recovery of the suspension through PEG-J or NJ tube and tested to determine the worst case scenario conditions (e.g. tubing material) which will be used for the equivalence testing below.

1. Determine comparative sedimentation depth (volume of sediment), particle size, and viscosity of aqueous gel suspension using 12 units each of the test and reference products as follows:

    a. Prepare the catheter tip syringe (60 mL), remove the syringe plunger, open the packet, and empty the content (about 30-50 mL) of one packet into the syringe. Insert the syringe plunger and place the syringe perpendicular to the bench with the tip up and record sedimentation depth immediately (0 min), 4 hrs, 8 hrs, and 16 hrs. Also, measure the viscosity of suspension at 0 hr, 4 hrs, 8 hrs, and 16 hrs.

    b. Determine the particle size for both carbidopa and levodopa in suspension.

    Provide all particle size data at the D10, D50, and D90 levels. You may use the markings on the syringe to note the sedimentation depth. Provide a qualitative description, e.g., homogeneous or sediment. Take photos of the content of the syringe at various intervals throughout the testing process. Determine particle size using laser diffraction method or any method that is sufficiently reproducible and sensitive.

2. Conduct the comparative recovery studies of the aqueous gel suspension from the French size 8.5 for J tube and size 10 for NJ tube using 12 units each of the test and the reference products. Determine the percentage of recovery, degradation (impurities), and delivery (flow) rate as follows:

    a. Remove the medication cassette reservoir containing drug product from the refrigerated conditions and connect to a pump that is used in in vivo BE study.

b. Connect the pump/cassette to the tubes (J or NJ tube) submerged in in a water bath, set at a target temperature range of 37°C.

c. Set the range of pump flow rate from 1 mL to 10 mL per hour and continuously infuse the drug product for 16 hours.

d. Collect samples in appropriate containers at the tube exit at 4, 8 and 16 hours of infusion for chemical testing, including assay for drug substances and impurities.

e. Collect the drug product delivered between 0 to 4 hours, 4 to 8 hours, and 8 to 16 hours for delivery rate assessment.

The pump, medication cassette, and all tubing normally positioned outside the body should be intentionally exposed to ambient room temperature and lighting to simulate the typical clinical use conditions. Determine the percentage of carbidopa and levodopa recovered at the tube exit relative to the initial dose for both the test (T) and the reference (R) products at 4, 8, and 16 hours using a validated analytical method. Also determine impurities of carbidopa and levodopa, such as DHPA (3,4-dihydroxypheylacetone), DHPPA (2-methyl-3-(3,4-dihydroxyphenyl)-propionic acid, and Hydrazine at the tube exit at 4, 8, and 16 hrs using a validated analytical method. Calculate delivery (flow) rates (mL/hr) between 0 to 4 hours, 4 to 8 hours, and 8 to 16 hours. The drug delivery rate accuracy should be assessed by comparing the calculate values to the delivery rates set at the pumps.

The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, you may increase the numbers of units used for this test.

3. Submit standard operating procedures for sedimentation, particle size, viscosity, recovery testing, delivery rate, and degradation (impurities) testing. Include details about the tube and syringe used (e.g., material, brand, size, etc.), the typical clinical use conditions of the tube, analytical site and testing dates, etc. for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (CV%) of each study in an Excel file. The photographs should be submitted to support your observations and results. Provide the pre-study and within-study assay validation report.

Conduct all the above testing on unexpired test and reference batches.