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Draft Guidance on Apomorphine Hydrochloride

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic apomorphine hydrochloride.

Active Ingredient: Apomorphine hydrochloride

Dosage Form; Route: Film; sublingual

Recommended Study: One study

1. Type of study: Fasting, bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 30 mg
   Subjects: Patients with Parkinson's disease (PD) who experience "off" episodes and are already receiving apomorphine hydrochloride sublingual film, 30 mg as the prescribed strength
   Additional comments:
   1. Subjects should present clinical response to levodopa treatment with "off" episodes and are taking apomorphine hydrochloride sublingual film, 30 mg as their prescribed strength for at least 4 weeks before screening. Subjects should receive a stable dose of levodopa/carbidopa and all other PD medications for

at least 4 weeks before screening (monoamine oxidase B inhibitors should be maintained at least 8 weeks prior to screening).

2. On the study day, subjects should take their usual morning dose of PD medications and then wait to take their next doses. Subjects should be ensured to be in the "off" state and then administer a sublingual dose of the test or reference product for the bioequivalence study. All PD medications should be held until 60 minutes after the dosing of the test or reference product.
3. Apomorphine treatment may be withheld for a limited duration of time (e.g., 1 day) to enable a sufficient washout period. Subjects should continue to take their usual doses of PD medications during this time. A time interval (e.g., 3 days) may be allowed between study periods.
4. Subjects who cannot tolerate an "off" state at any point during the study should receive levodopa and/or other PD medications as a rescue therapy.
5. Safety parameters (e.g., blood pressure) and occurrence of "off" episodes should be monitored during the study.
6. Exclude patients with expected changes in concomitant medications (e.g., addition or discontinuation of PD medications, or drugs known to affect the pharmacokinetics of apomorphine) during the study. Concomitant antiemetic medications (such as trimethobenzamide) may be used as recommended by the approved labeling of the reference product during the study.

Analyte to measure: Apomorphine in plasma

Bioequivalence based on (90% CI): Apomorphine

Waiver request of in vivo testing: The 10 mg, 15 mg, 20 mg, 25 mg strengths of the sublingual film may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 30 mg strength sublingual film, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the sublingual film formulation across all strengths.

NOTE: The proportional similarity of the sublingual film formulation across all strengths means (i) that the amounts of active and inactive ingredients per unit surface area are identical for the different strengths of the test product, and (ii) that the ratios of the surface areas of each strength of the test product compared to the 30 mg strength of the test product are the same as the corresponding ratios for the surface areas of each strength of the reference product compared to the 30 mg strength of the reference product.

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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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