Recommended Feb 2022

Contains Nonbinding Recommendations
Draft – Not for Implementation

Draft Guidance on Apomorphine Hydrochloride
February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug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.

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.

The contents of this document do not have the force and effect of law and are not meant to bind
the public in any way, unless specifically incorporated into a contract. This document is intended
only to provide clarity to the public regarding existing requirements under the law. FDA
guidance documents, including this guidance, should be viewed only as recommendations, unless
specific regulatory or statutory requirements are cited. The use of the word should in FDA
guidances means that something is suggested or recommended, but not required.

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/](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.

**Unique Agency Identifier:** PSG_210875