*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Dihydroergotamine Mesylate**

**February 2023**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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**Active Ingredient:** Dihydroergotamine mesylate

**Dosage Form; Route:** Spray, metered; nasal

**Strength:** 0.725 mg/spray

**Recommended Study:** One in vivo bioequivalence study with pharmacokinetic endpoints

FDA recommends the following in vivo study to establish bioequivalence of the test (T) and reference (R) nasal sprays containing dihydroergotamine mesylate.

**In vivo bioequivalence study with pharmacokinetic endpoints:**

FDA recommends the following pharmacokinetic study to establish bioequivalence (BE) between the T and R product:

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 0.725 mg/spray
   Dose: 1.45 mg (one spray in each nostril)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Subjects should adhere to the R drug product labeling for administration.

**Analyte to measure:** Dihydroergotamine in plasma

**Equivalence based on:** AUC and $C_{max}$ for dihydroergotamine. The 90% confidence intervals for the geometric mean T/R ratios of AUC and $C_{max}$ should fall within the limits of 80.00 - 125.00%.

**Additional information:**

Device:
The reference listed drug (RLD) is presented as a co-packaged kit containing a glass vial of the drug product and the nasal spray device, which is the device constituent.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device including:

- Single-use, single-dose design
- Manually activated
- Metered spray
- Requires priming

User interface assessment:
An Abbreviated New Drug Application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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