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Draft – Not for Implementation

Draft Guidance on Diazepam

February 2024

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Active Ingredient:	Diazepam
Dosage Form:	Spray
Route:	Nasal
Strengths:	5 mg/spray, 7.5 mg/spray, 10 mg/spray
Recommended Studies:	Two options: (1) five in vitro bioequivalence studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: Five in vitro bioequivalence studies

To demonstrate bioequivalence by this option, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RS product to satisfy no difference in inactive ingredients.

[1] Q1 (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the RS formulation.

[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the RS formulation.

FDA recommends that prospective applicants conduct the following in vitro bioequivalence studies on samples from each of three or more batches of the T product and three or more batches of the RS product, with no fewer than 10 units from each batch.[3] FDA recommends that three primary stability batches be also used to demonstrate in vitro bioequivalence. The three batches of the T product should be manufactured from, at minimum, three different batches of the drug substance, three different batches of critical excipients, and three different batches of the device components (e.g., pump and actuator) proposed for the final device configuration of the commercial product. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The following in vitro bioequivalence tests are recommended:

1. Single actuation content (SAC)
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Nasal Metered Spray* (NDA 020121)[a] for recommendations on design and equivalence criteria for the aforementioned in vitro bioequivalence studies, and general recommendations on the conduct of the in vitro bioequivalence studies and data submission.[4]

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Strength: 10 mg/spray
   Dose: 10 mg, administered as one spray in one nostril
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: (1) Subjects should adhere to the reference listed drug (RLD) product labeling for administration. (2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of diazepam in plasma. Ensure that there are adequate washout periods between treatments in the crossover studies due to the long terminal elimination half-life. Also, consider using a parallel study design due to the long half-life. For long half-life drug products with low intra-subject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (t_{max}).

Analyte to measure: Diazepam in plasma

[3] If bioequivalence of the 10 mg/spray strength is acceptable, then drug in small particles/droplets and plume geometry bioequivalence tests may not be needed for the 5 mg/spray and 7.55 mg/spray strengths provided both of these strengths of the drug product are manufactured without changing the actuator and metering valve or pump (other than dip tube, due to different volumes of product or other factors) used in the 10 mg/spray product. With the exception of the reduced testing, the Agency recommends the same protocols and the acceptance criteria used to establish bioequivalence of the 10 mg/spray product be used for the 5 mg/spray and 7.5 mg/spray products.
[4] Recommendations for testing at various lifestages are not relevant for this product given it is a single-use configuration.

Equivalence based on: AUC and C_{max} for diazepam. 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%.

Waiver of in vivo testing: 5 mg/spray and 7.5 mg/spray strengths, based on (i) acceptable bioequivalence study on the 10 mg/spray strength and (ii) proportional similarity of the formulations across all strengths

Additional information:

Device:
The RLD is presented as one or two single-use nasal spray devices. The nasal spray device is the device constituent part.

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 format
- No priming

User interface assessment:
An abbreviated new drug application 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*.[b]

Document History: Recommended November 2020; Revised February 2024

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[a] For the most recent version of the product-specific guidance, check the FDA product-specific guidance website at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.