Draft Guidance on Diazepam

Active Ingredient: Diazepam

Dosage Form; Route: Spray; nasal

Strengths: 5 mg/spray
7.5 mg/spray
10 mg/spray

Recommended Studies: Two Options: in vitro or in vivo studies

FDA recommends the following in vitro or in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing diazepam.

In Vitro Option

If the test (T) formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference (R) formulation, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for approval in an abbreviated new drug application (ANDA) (as demonstrated by comparative analyses further described below), BE of the T diazepam nasal spray product to the R diazepam nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that prospective applicants conduct the following in vitro BE studies on samples from each of three or more batches of the T product and three or more batches of the R product with no fewer than 10 units from each batch. FDA recommends that three primary stability batches also be used to demonstrate in vitro BE. 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 BE tests are recommended:

1. Single actuation content

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.

2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry

Additional Comments: Refer to the product-specific guidance for *Fluticasone Propionate Nasal Spray Metered* for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.[3]

In Vivo Option

If the T formulation is not Q1 and Q2 the same as the R formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for approval in an ANDA (as demonstrated by comparative analyses further described below), the following PK study is recommended to establish BE between the T and R product:

Type of Study: Fasting
Design: Single-dose, two-way crossover
Strength: 10 mg/spray
Dose: 10 mg of diazepam (10 mg/spray x 1 spray in one nostril)
Subjects: Adult males and non-pregnant, non-lactating females, general population
Additional Comments**:** (1) Subjects should adhere to the R 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

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.

[3] Specific recommendations for in vitro BE testing at various lifestages are not relevant for this product given it is a single-use configuration.

Additional Information

Device:
Prospective applicants should refer to the FDA guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

- Single-unit dose design
- External operating principles and external critical design attributes of the R product
- Size and shape of the R product