

Draft Guidance on Zolmitriptan

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Zolmitriptan

Dosage Form; Route: Spray; Nasal

Strengths: 2.5 mg/spray
5 mg/spray

Recommended Studies: Two options: In vitro or In vivo

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

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 comparable to that of the R product, BE of the T zolmitriptan unit dose nasal spray product to the R zolmitriptan unit dose nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that 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.³ FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The batches should be prepared from three different batches of the same device (pump and actuator) components. The following in vitro BE tests are recommended:

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

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 $\pm 5\%$ of those used in the R product.

³ If bioequivalence of the 5 mg/spray strength is acceptable, then drug in small particles/droplets and plume geometry BE tests may not be needed for the 2.5 mg/spray strength provided the 2.5 mg/spray product is manufactured without changing critical device attributes (e.g., the actuator and metering valve or pump, other than diptube, due to different volumes of product or other factors) used in 5 mg/spray product. With the exception of the reduced testing, FDA recommends the same protocols and the acceptance criteria used to establish BE of the 5 mg/spray product be used for the 2.5 mg/spray product.

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.⁴

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 study is recommended to establish BE between the T and R products:

Type of study: Fasting

Design: Single-dose, two-way crossover

Strength: 5 mg/spray x 1 spray (5 mg dose)

Subjects: Males and nonpregnant females, general population

Additional Comments: Subjects should adhere to the R product labeling for administration.

Analyte to measure (in appropriate biological fluid): zolmitriptan and its active metabolite, N-desmethylzolmitriptan, in plasma

Equivalence based on: AUC and C_{\max} for zolmitriptan. 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: 2.5 mg/spray strength, based on (i) acceptable bioequivalence study on the 5 mg/spray strength, and (ii) proportional similarity of the formulations across both strengths.

Additional Information

Device:

Sponsors should refer to FDA's guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies* (January 2017), 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 applicants consider the following characteristics of the R product when designing the T product:

⁴ Specific recommendations for the in vitro BE testing at various life stages are not relevant for this product, given it is a single-use configuration.

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

In addition, studies should be conducted to support the functionality, accuracy, and robustness of the proposed T product.⁵

⁵ Refer to the FDA Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (July 2002) for relevant principles regarding studies to support nasal spray devices.