

## **Draft Guidance on Zolmitriptan**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Zolmitriptan

**Dosage Form; Route:** Spray; Nasal

**Recommended Studies:** 2 options: In vivo or In vitro

### **I. In Vivo Option:**

If the test product is **not** qualitatively (Q1) and quantitatively (Q2) the same as the reference product, the following study is recommended to document bioequivalence of the test product to the reference product.

Type of study: Fasting

Design: Single-dose, two-way crossover in-vivo

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

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments:

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**Analytes to measure (in appropriate biological fluid):** Zolmitriptan and its active metabolite, N-desmethylzolmitriptan in plasma.

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

**Bioequivalence based on (90% CI):** Zolmitriptan

**Waiver request of in-vivo testing:** 2.5 mg/spray based on acceptable (i) bioequivalence studies on the 5 mg/spray strength, and (ii) proportional similarity of the formulations.

**Dissolution test method and sampling times:** Not Applicable

**Additional Information:**

1. While comparative in vitro studies are not required, in vitro studies outlined in the 2002 Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>) should be submitted for Chemistry, Manufacturing, and Controls evaluation.
2. Per 21 CFR 314.94(a)(9)(v), a generic Zolmitriptan nasal spray product may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. In addition, due to concerns of local irritation caused by inactive ingredients change, the firm should provide supportive information.

## II. In Vitro Option

If the test product is qualitatively (Q1) and quantitatively (Q2) the same as the reference product, then bioequivalence may be documented by an in vitro approach in lieu of an in vivo approach. Equivalent in vitro performance of the test product to the reference product should be established for both strengths (5 mg/spray and 2.5 mg/spray). The current FDA recommendations for documenting equivalent spray device performance via in vitro testing may be found in the draft guidance “Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action”. The guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070111.pdf> under Biopharmaceutics Draft (April 2003). As specified in the guidance, in vitro bioequivalence of the higher strength should be characterized by the full set of tests. If bioequivalence of the higher strength is acceptable, then abbreviated in vitro testing is recommended to document bioequivalence of the lower strength test product to the lower strength reference product.

**Waiver request of in vitro testing:** Not Applicable

**Dissolution test method and sampling times:** Not Applicable

**Additional Information:** Not Applicable