

Draft Guidance on Mometasone Furoate; Olopatadine Hydrochloride

August 2023

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Active Ingredients:	Mometasone furoate; Olopatadine hydrochloride
Dosage Form:	Spray, metered
Route:	Nasal
Strength:	0.025 mg/spray; 0.665 mg/spray
Recommended Studies:	Two options: (1) eight in vitro bioequivalence studies or (2) six in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

FDA recommends the following in vitro or in vitro and in vivo studies to establish bioequivalence of test (T) and reference (R) nasal spray products containing mometasone furoate and olopatadine hydrochloride. The recommendations provided here supersede information provided in the most recent version of the FDA draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.^a

I. Option 1: Eight in vitro bioequivalence studies

To be eligible for this recommended option to demonstrate bioequivalence, the T product formulation should be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the R product formulation, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an abbreviated new drug application (ANDA).

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.

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 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 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
6. Prime and repriming
7. Drug particle size distribution
8. Dissolution

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Fluticasone Propionate Nasal Metered Spray* (NDA 020121)^b 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.

II. Option 2: Six in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

If the T product formulation is not Q1 and Q2 the same as the R product formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an ANDA, then in vitro bioequivalence studies #1 through #6 (as described in Option 1), and the following in vivo studies are recommended to establish bioequivalence between the T and R products:

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
Design: Single-dose, two-way crossover
Strength: 0.025 mg/spray; 0.665 mg/spray
Dose: Minimum number of sprays that is sufficient to characterize a pharmacokinetic profile by using a sensitive analytical method.
Subjects: Healthy adult males and non-pregnant, non-lactating females
Additional comments: Follow the reference listed drug (RLD) labeling for the method of drug administration. The analytical method should have sufficient sensitivity to adequately quantify the concentration of mometasone furoate and olopatadine in plasma. A Bio-IND is required prior to conduct of the pharmacokinetic study if the dose exceeds the maximum labeled single dose.

Analytes to measure: Mometasone furoate and olopatadine in plasma

Equivalence based on: AUC and C_{\max} for mometasone furoate and olopatadine. 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%.

One comparative clinical endpoint bioequivalence study:

These recommendations are specific to this product and may not be appropriate for comparative clinical endpoint bioequivalence studies of any other product, including any other dosage form or strength of mometasone furoate and olopatadine hydrochloride.

1. Type of study: Comparative clinical endpoint bioequivalence study
Design: Randomized, double-blind, three-arm, placebo-controlled, parallel group
Strength: 0.025 mg/spray; 0.665 mg/spray
Dose: 0.1 mg/2.66 mg twice daily, administered as two sprays in each nostril
Subjects: Adult males and non-pregnant, non-lactating females with seasonal allergic rhinitis (SAR)
Additional comments: Specific recommendations are provided below.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a single comparative clinical endpoint bioequivalence study in the treatment of SAR consisting of 2 periods: a 7-day, single-blinded, placebo run-in period (Study Days -7 to -1) to establish a baseline and to identify placebo responders, followed by a 14-day treatment period (Study Days 1 to 14). Prime each product as per the RLD labeling prior to initial dosing. During the placebo run-in period, all subjects are to receive the placebo vehicle administered as two sprays in each nostril once daily for 7 days. All subjects who qualify after the placebo run-in period are to be randomized to receive the T product, R product, or placebo (vehicle) control during the treatment period, administered as two sprays in each nostril once daily for 14 days. The primary endpoint is the difference in the mean change in reflective total nasal symptom scores from baseline through the treatment period.
2. A multi-center study is recommended to avoid potential investigator bias.
3. A double dummy design is not recommended for study blinding due to a concern that the doubled fluid volume may result in washing the drug from its nasal deposition sites, potentially resulting in an altered safety and efficacy profile.
4. Inclusion criteria (the prospective applicant may add additional criteria):
 - a. Males and non-pregnant, non-lactating females, 18 years of age and older. For female subjects of childbearing potential: agreement to practice an approved method of birth control.
 - b. History of SAR for at least 2 years.

- c. A positive test for relevant specific allergens (e.g., allergen skin test).
 - d. Demonstration of significant symptoms during screening and randomization visits, measured by a reflective total nasal symptom score (rTNSS) of, for example, at least 6 at the time of enrollment (see items 8 and 9).
5. Exclusion criteria (the prospective applicant may add additional criteria):
- a. Pregnant or lactating or planning to become pregnant during the study period
 - b. Asthma, with the exception of mild intermittent asthma.
 - c. Active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal, bacterial, viral, or parasitic infections.
 - d. Presence of glaucoma, cataracts, ocular herpes simplex, conjunctivitis, or other eye infection.
 - e. Presence of any nasal mucosal erosion, nasal septal ulcers, or septum perforation on focused nasal examination at screening or randomization.
 - f. Recent nasal or sinus surgery or nasal trauma.
 - g. Other nasal disease(s) likely to affect deposition of intranasal medication, such as acute or chronic sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities.
 - h. Presence or history of any clinically significant condition that, in the opinion of the investigator, would compromise the safety of the subject or the conduct of the study.
 - i. Respiratory tract infection requiring antibiotics within 4 weeks prior to screening.
 - j. Use of any investigational drug within 30 days prior to screening.
 - k. Initiation of immunotherapy or its dose escalation for 1 month prior to screening and during the study (it is acceptable if subjects are on a stable regimen for at least 30 days prior to screening and they should maintain the same dose during the study).
 - l. Use of any prohibited medications and treatments (e.g., anti-allergy therapy as antihistamines, systemic or intranasal decongestants, leukotriene antagonists, corticosteroids, other nasal therapies, central nervous system depressants, potent cytochrome P450 3A4 inhibitors such as ketoconazole, etc.) prior to screening [the sponsor should provide a list of treatments with justification/rationale provided for duration of the washout period prior to screening].
 - m. Planned travel outside the study area from the time of enrollment to completion of the study.
 - n. Any hypersensitivity to mometasone furoate, olopatadine hydrochloride, similar drugs, or any of the study medications or inactive ingredients.
6. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as anti-allergy therapy as antihistamines, systemic or nasal decongestants, leukotriene antagonists, corticosteroid therapy (parenteral, intranasal, oral, inhaled or potent topical), anti-IgE antibodies (e.g., omalizumab), immunosuppressive therapy, central nervous system depressants (e.g., alcohol) and potent cytochrome P450 3A4 inhibitors such as ketoconazole.

7. Subjects should be advised not to drive, operate machinery, or do anything that needs alertness until they know that the use of the products affect them.
8. Subjects should self-score their symptoms twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo run-in period and the 14-day randomized treatment period. Scoring should be made immediately prior to each dose, to reflect the previous 12 hours (reflective scores) and how the subject is feeling at the time of evaluation, i.e., at the end of dosing interval (instantaneous scores). Each of the following symptom should be scored using the following scale:
 - a. Symptoms: Runny nose, sneezing, nasal itching, and congestion.
 - b. Scoring Scale: The following is an example of an acceptable scale. Each score should be objectively defined.

Table 1. Sample Scoring Scale

Score	Description
0	absent (no symptom evident)
1	mild (symptom clearly present, but minimal awareness; easily tolerated)
2	moderate (definite awareness of symptom that is bothersome but tolerable)
3	severe (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

9. Total nasal symptom score (TNSS) is the sum of each individual symptom rating for runny nose, sneezing, nasal itching, and congestion.
10. Baseline mean rTNSS is the mean of the final seven scores from the placebo run-in period. The final seven scores from the placebo run-in period consist of the AM and PM scores on Days -3, -2, and -1 and the AM score (prior to drug dosing) on Day 1 of the 14-day randomized treatment period.
11. Placebo responders should be excluded from the study to increase the ability to show a significant difference between active and placebo treatments and to increase sensitivity to detect potential differences between active products.
12. Treatment mean rTNSS is the average of 27 scores from the randomized treatment period. The 27 scores consist of the PM score on Day 1 and the AM and PM scores on Days 2 to 14.
13. The recommended primary endpoint is the change from the baseline mean rTNSS to the treatment mean rTNSS expressed in absolute units rather than percent change from baseline.
14. FDA recommends that each of the T and R batches used in the comparative clinical endpoint bioequivalence study be at least one of the three batches used for the in vitro bioequivalence studies and the in vivo bioequivalence study with pharmacokinetic endpoints.

15. FDA recommends using a statistical model for the endpoint data that takes into account baseline values. If the study was conducted at multiple clinical centers, the center should also be considered in the data analysis.
16. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)^b for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
17. Refer to the Study Data Standards Resources website
<https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

Additional information:

Device:

The RLD is presented in a bottle with a nasal pump and actuator. The pump with actuator 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 product when designing the T device including:

- Metered, multi-dose format
- Same number of doses

User interface assessment:

An 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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Unique Agency Identifier: PSG_211746

^a For the most recent version of a guidance, check the FDA guidance website at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

^b 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>.