# Fluticasone Propionate Nasal Spray

## DEFINITION

Fluticasone Propionate Nasal Spray is a white, opaque suspension of Fluticasone Propionate in water. It is supplied in a form suitable for nasal administration. It contains NLT 95.0% and NMT 115.0% of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

## IDENTIFICATION

• **A. INFRARED ABSORPTION** ⟨197M⟩

**Sample:** Transfer 30 g of Nasal Spray equally into two 50-mL centrifuge tubes. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 min. Centrifuge at 3500 rpm for 10 min, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 min. Centrifuge at 3500 rpm for 10 min, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 min. Centrifuge at 3500 rpm for 10 min, and discard the supernatant. To one tube add 10 mL of methanol. Shake to disperse the residue, and transfer to the other tube. Shake the other tube for 1 min. Centrifuge at 3500 rpm for 10 min. Decant the supernatant into an agate mortar. Evaporate the methanol either by carefully blowing dry with compressed air or nitrogen, or by allowing the methanol to evaporate naturally. If using an air or nitrogen line, use a suitable in-line filter to avoid contamination. Allow the residue to dry overnight in a desiccator over silica gel.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

• **PROCEDURE**

**Diluent:** Acetonitrile and 0.001 M hydrochloric acid (60:40)

**Buffer:** 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.5 ± 0.05.

**Mobile phase:** Methanol, acetonitrile, and *Buffer* (50:15:35)

**System suitability solution:** 50 µg/mL of USP Phenylethyl Alcohol RS and 10 µg/mL of USP Fluticasone Propionate Nasal Spray Resolution Mixture RS in *Diluent*

**Standard solution:** 10 µg/mL of USP Fluticasone Propionate RS in *Diluent*

**Sample solution:** Nominally 10 µg/mL prepared as follows: Transfer an amount of the Nasal Spray containing 0.5 mg of fluticasone propionate to a 50-mL volumetric flask, add about 40 mL of *Diluent*, and sonicate the flask for 10 min. Dilute with *Diluent* to volume, and shake. Allow to stand for 10 min until the supernatant is a clear solution. Inject the clear supernatant into the chromatograph.

**Chromatographic system**

(See *Chromatography* ⟨621⟩, *System Suitability*.)

**Mode:** LC

**Detector:** UV 210 and 239 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection size:** 20 µL

**System suitability**

[NOTE—Record the peak areas at 210 nm for 5 min, then change the wavelength to 239 nm and record the peak areas.]

**Samples:** *System suitability solution* and *Standard solution*

Record the chromatogram at 210 nm for 5 min and then change the wavelength to 239 nm.

[NOTE—The relative retention times for phenylethyl alcohol, fluticasone propionate, and fluticasone propionate related compound D are about 0.42, 1.0, and 1.10, respectively.]

**Suitability requirements**

**Resolution:** NLT 1.5 between fluticasone propionate and fluticasone propionate related compound D, *System suitability solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the label claim of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Nasal Spray taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Fluticasone Propionate RS in the *Standard solution* (µg/mL)
$C_U$ = nominal concentration of Fluticasone Propionate in the *Sample solution* (µg/mL)

**Acceptance criteria:** 95.0%–115.0%

## OTHER COMPONENTS

• **CONTENT OF PHENYLETHYL ALCOHOL**

**Diluent, Mobile phase, System suitability solution, Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*.

**Standard solution:** 0.05 mg/mL of USP Phenylethyl Alcohol RS in *Diluent*

**Sample solution:** Transfer 1.0 g of the Nasal Spray to a 50-mL volumetric flask. Add about 40 mL of *Diluent*, and sonicate for 10 min until supernatant is clear. Use the clear supernatant for analysis.

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the quantity, in mg/g, of phenylethyl alcohol in the portion of Nasal Spray taken:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/W)$$

$r_U$ = peak response of phenylethyl alcohol from the *Sample solution*
$r_S$ = peak response of phenylethyl alcohol from the *Standard solution*
$C_S$ = concentration of USP Phenylethyl Alcohol RS in the *Standard solution* (mg/mL)
$V$ = volume of the *Sample solution*, 50 mL
$W$ = weight of the Nasal Spray in the *Sample solution* (g)

**Acceptance criteria**

For 50 sprays: 1.75 mg/g–2.63 mg/g
For 120 sprays: 1.88 mg/g–2.63 mg/g

***Change to read:***

• **CONTENT OF BENZALKONIUM CHLORIDE**

**Buffer:** 250 mg/mL of citric acid. Adjust the solution with 2 N sodium hydroxide to a pH of 3.5 ± 0.05.

**Standard solution:** 200 µg/mL [0.02% (w/w)] of USP Benzalkonium Chloride RS in water

**Docusate sodium titrant:** Dissolve 0.22 g of USP Docusate Sodium RS in 100 mL of warm water. Dilute with water to make 1000 mL.

**Eosin Y indicator:** Dissolve 25 mg of eosin Y in 50 mL of acetone. Add 450 mL of chloroform and 5.0 ± 0.5 g of citric acid. Shake thoroughly until no discoloration occurs. Filter

the mixture to remove any undissolved citric acid. Store in an amber bottle.

**Titer value of docusate sodium:** Pipet 10 mL of the *Standard solution* into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator*, and 2 mL of *Buffer.* Insert the stopper into the flask, and shake, releasing any build-up of pressure. Titrate with *Docusate sodium titrant* with vigorous shaking to a point when pink coloration is discharged from the chloroform layer. Perform a blank determination, substituting 10 mL of water for the *Standard solution*, and make any necessary correction (see *Titrimetry* ⟨541⟩).

Calculate the titer value of *Docusate sodium titrant*, in µg/mL, of benzalkonium chloride:

$$\text{Result} = C_S \times (V_S/V_D)$$

$C_S$ = concentration of USP Benzalkonium Chloride RS in the *Standard solution* (µg/mL)
$V_S$ = volume of the *Standard solution*, 10 mL
$V_D$ = volume of *Docusate sodium titrant* used in the titration of the *Standard solution* (mL)

**Analysis**

**Sample:** 10 g of Nasal Spray

Transfer the *Sample* into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator*, and 2 mL of *Buffer*. Repeat the procedure as given above for the *Standard solution*. To clarify the endpoint, place the flask in an ultrasonic bath for 1–2 min to separate the chloroform layer from the aqueous phase. Perform a blank determination.

Calculate the concentration of benzalkonium chloride, in µg/g, in the portion of Nasal Spray taken:

$$\text{Result} = TV/W$$

$T$ = titer value of *Docusate sodium titrant*
$V$ = volume of *Docusate sodium titrant* used in the titration of the Nasal Spray (mL)
$W$ = weight of the portion of Nasal Spray taken (g)

**Acceptance criteria:** •140–220 µg/g• (RB 1-Feb-2011)

## PERFORMANCE TESTS

• **Delivered Dose Uniformity** (within container)

**Diluent:** Acetonitrile and 0.001 M hydrochloric acid (60:40)

**Buffer:** 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.5 ± 0.05.

**Mobile phase:** Methanol, acetonitrile, and *Buffer* (50:15:35)

**System suitability solution:** 5 µg/mL of USP Fluticasone Propionate Nasal Spray Resolution Mixture RS in *Diluent*

**Standard solution:** 4 µg/mL of USP Fluticasone Propionate RS in *Diluent*

**Sample solution:** Wipe the pump clean. Shake the bottle for 30 s, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations (1 dose) into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after collecting two actuations. Discharge actuations 3–48 (50-spray pack) or 3–118 (120-spray pack) to waste. Wipe the bottle clean, and collect the last two actuations (49 and 50 or 119 and 120) in a second 25-mL volumetric flask. Turn the flask to the upright position immediately after each actuation, and insert the stopper into the flask. Add 20 mL of *Diluent* to each flask, and shake well for 10 min to disperse the suspension. Dilute with *Diluent* to volume, and mix thoroughly. Allow the flask to stand until the excipients have settled. Inject the clear supernatant. Repeat this procedure with 4 additional bottles.

**Chromatographic system**

(See *Chromatography* ⟨621⟩*, System Suitability*.)

**Mode:** LC

**Detector:** UV 239 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection size:** 50 µL

**System suitability**

**Samples:** *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for fluticasone propionate and fluticasone propionate related compound D are about 1.0 and 1.10, respectively.]

**Suitability requirements**

**Resolution:** NLT 1.5 between fluticasone propionate and fluticasone propionate related compound D, *System suitability solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the label claim of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in each dose:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Fluticasone Propionate RS in the *Standard solution* (µg/mL)
$C_U$ = nominal concentration of the *Sample solution* (µg/mL)

**Acceptance criteria:** The mean dose delivered from 10 doses is within 85%–115% of the label claim. NMT 1 dose is outside 80%–120% of the label claim. No doses are outside 75%–125% of the label claim. If 2 or 3 doses are outside outside 80%–120% of the label claim, test an additional 10 bottles. The mean dose delivered from 30 doses is within 85%–115% of the label claim. NMT 3 doses are outside 80%–120% of the label claim. No doses are outside 75%–125% of the label claim.

• **Delivered Dose Uniformity** (within batch)

**Diluent, Buffer, Mobile phase, System suitability solution, Standard solution, Chromatographic system,** and **System suitability:** Prepare as directed in the test for *Delivered Dose Uniformity (within container).*

**Sample solution:** Wipe the pump clean. Shake the bottle for 30 s, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after collecting two actuations (1 dose). Repeat this procedure with 9 additional bottles.

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the label claim of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in each dose:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Fluticasone Propionate RS in the *Standard solution* (µg/mL)
$C_U$ = nominal concentration of the *Sample solution* (µg/mL)

**Acceptance criteria:** The mean dose delivered from 10 doses is within 85%–115% of the label claim. NMT 1 dose is outside 80%–120% of the label claim. No doses are outside 75%–125% of the label claim. If 2 or 3 doses are outside 80%–120% of the label claim, test an additional 20

bottles. The mean dose delivered from 2 actuations in the beginning of the 30 bottles (30 doses) is within 85%–115% of the label claim. NMT 3 doses are outside 80%–120% of the label claim. No doses are outside 75%–125% of the label claim.

## IMPURITIES

- **ORGANIC IMPURITIES**

**Diluent:** Acetonitrile and 0.001 M hydrochloric acid (60:40)
**Solution A:** Methanol and acetonitrile (77:23)
**Buffer:** 1.2 g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.4 ± 0.1.
**Mobile phase:** *Solution A* and *Buffer* (60:40)
**System suitability solution:** 0.1 mg/mL of USP Fluticasone Propionate Related Compounds Mixture RS and 0.5 mg/mL of USP Phenylethyl Alcohol RS in *Diluent*
**Control solution:** 0.5 mg/mL of USP Phenylethyl Alcohol RS and 0.08 mg/mL of USP Benzalkonium Chloride RS in a mixture of *Diluent* and water (4:1)
**Sample solution:** 0.2 g/mL of Nasal Spray in *Diluent*. Shake the flask vigorously to dissolve. Pass through a 0.5-µm filter.
**Chromatographic system**
(See *Chromatography* ⟨621⟩*, System Suitability*.)
**Mode:** LC
**Detector:** UV 239 nm
**Column:** 4.6-mm × 25-cm; 5-µm packing L1
**Column temperature:** 40°
**Flow rate:** 1.5 mL/min
**Injection size:** 50 µL
**System suitability**
**Sample:** *System suitability solution*
[NOTE—See *Table 1* for the relative retention times.]
**Suitability requirements**
**Resolution:** NLT 1.5 between fluticasone propionate related compound F and phenylethyl alcohol. NLT 2 between fluticasone propionate related compound D and fluticasone propionate
**Analysis**
**Samples:** *System suitability solution*, *Control solution*, and *Sample solution*
Calculate the percentage of each impurity in the portion of Nasal Spray taken:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$ = peak response for each impurity from the *Sample solution*
$r_T$ = sum of all the peak responses from the *Sample solution*, excluding the peaks obtained from the *Control solution*

**Acceptance criteria:** See *Table 1*.

**Table 1**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| *S*-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate/*S*-Fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-3,6-dioxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate | 0.7 | 0.3 |
| Fluticasone propionate related compound D | 1.1 | 0.3 |
| 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid-6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl ester | 2.1 | 0.3 |
| Any unspecified related impurities | — | 0.2 |
| Total impurities | — | 1.5 |

## SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩**:** It meets the requirements of the tests for absence of *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, and *Pseudomonas aeruginosa*. The total aerobic microbial count does not exceed 25 cfu/mL, and the total combined molds and yeasts count does not exceed 25 cfu/mL.
- **pH** ⟨**791**⟩**:** 5.0–7.0
- **PARTICLE SIZE**

**Analysis:** Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400× magnification. Drug substance particles are irregular in shape, whereas the excipient particles are elongated and angular. Record the number of individual drug substance particles that are less than 5 µm in diameter, greater than 5 µm but less than 15 µm in diameter, and greater than 15 µm in diameter. Calculate the percentage of each category by number.
**Acceptance criteria:** See *Table 2*.

**Table 2**

| Particle Size | Acceptance Criteria |
|---|---|
| <5 µm | NLT 98% |
| >5 µm – <15 µm | NMT 1.8% |
| >15 µm | NMT 0.2% |

- **FOREIGN PARTICULATES**

**Analysis:** Shake the required number of bottles to ensure uniformity. Remove the pump system carefully to minimize contamination of the sample. Collect about 100 g of Nasal Spray, and pass it through a wetted 250-µm screen. Rinse each bottle with a portion of water equal to twice the volume of each bottle. Pass the rinse through the 250-µm screen. Visually observe the screen and filtrate for any foreign particulates. Also examine the screen under a microscope using transmitted light.
**Acceptance criteria:** No foreign particulates greater than 250 µm are visible.

- **DROPLET SIZE DISTRIBUTION:** Determine using a validated laser diffraction technique and method that measures the volume diameters of droplets. In preparation shake the bottle to ensure product uniformity. Prime the pump by discharging a predetermined (refer to the product label) number of actuations to waste, at which time a fine mist should appear. Measure and record the average of three sprays per bottle, and report the mean diameter defining the population of particles, by volume, below 10% ($D_{10}$), 50% ($D_{50}$), and 90% ($D_{90}$) of five bottles.
- **SPRAY PATTERN:** Determine the spray pattern using a validated method that measures the size of the pattern. Gently

shake the bottle to ensure product uniformity. Prime the pump by discharging a predetermined number (refer to the product label) of actuations to waste, at which time a fine mist should appear. Measure and record the average of two sprays per bottle and report the longest axis (x axis), and the ratio of longest to shortest axes (x/y ratio) of two bottles.

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store between 4° and 30°.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Benzalkonium Chloride RS

USP Docusate Sodium RS

USP Fluticasone Propionate RS

USP Fluticasone Propionate Nasal Spray Resolution Mixture RS

This Reference Standard is a mixture of fluticasone propionate and fluticasone propionate related compound D, and the chemical names for both are given below:

*Fluticasone propionate: S*-Fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

*Fluticasone propionate related compound D: S*-Methyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

USP Fluticasone Propionate Related Compounds Mixture RS

This Reference Standard is a mixture of fluticasone propionate and fluticasone propionate related compounds D and F, and the chemical names for all are given below:

*Fluticasone propionate: S*-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

*Fluticasone propionate related compound D: S*-Methyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

*Fluticasone propionate related compound F:* 6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid.

USP Phenylethyl Alcohol RS