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*Add the following:*

# ▲Budesonide Nasal Spray

## DEFINITION

Budesonide Nasal Spray is an aqueous buffered suspension of Budesonide, supplied in a form suitable for nasal administration and contains suitable preservatives. It contains NLT 90.0% and NMT 110.0% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).

## IDENTIFICATION

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

• **B.** The UV spectrum of the budesonide peak of the *Sample solution* exhibits a maximum and minimum at the same wavelengths as those of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

• **Procedure**

**Mobile phase:** Acetonitrile and water (70:30)

[Note—Use low-actinic glassware for preparation of the *Standard solution* and *Sample solution*.]

**Standard solution:** 0.05 mg/mL of USP Budesonide RS in acetonitrile

**Sample solution:** Nominally 0.05 mg/mL of budesonide in acetonitrile prepared as follows. Prepare a composite by mixing NLT 5 containers of Nasal Spray in a suitable container. Weigh a quantity of the composite solution into a suitable volumetric flask. Dilute with acetonitrile to volume.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 245 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

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

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 2 times the retention time of budesonide

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 1.0%

**Analysis**

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

Calculate the percentage of the labeled amount of budesonide ($C_{25}H_{34}O_6$) in the portion of Nasal Spray taken:

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

$r_U$ = peak response of budesonide from the *Sample solution*

$r_S$ = peak response of budesonide from the *Standard solution*

$C_S$ = concentration of USP Budesonide RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of budesonide in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

## OTHER COMPONENTS

• **Content of Potassium Sorbate**

Perform this test if potassium sorbate is a component in the Nasal Spray.

**Buffer:** 1.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to pH 3.0.

**Mobile phase:** Acetonitrile and *Buffer* (40:60)

**Standard solution:** 0.04 mg/mL of USP Potassium Sorbate RS in water

**Sample solution:** Nominally 0.04 mg/mL of potassium sorbate in water prepared as follows. Prepare a composite by mixing NLT 5 containers of Nasal Spray in a suitable container. Transfer 1.0 mL of the well-mixed composite solution to a 25-mL volumetric flask containing 10 mL of water. Add 5 drops of 0.5 N hydrochloric acid. Dilute with water to volume. Centrifuge for about 10 min at about 3600 rpm, and use the clear solution.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 260 nm

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

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 4 times the retention time of potassium sorbate

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the percentage of the labeled amount of potassium sorbate ($C_6H_7KO_2$) in the portion of Nasal Spray taken:

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

$r_U$ = peak response of potassium sorbate from the *Sample solution*

$r_S$ = peak response of potassium sorbate from the *Standard solution*

$C_S$ = concentration of USP Potassium Sorbate RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of potassium sorbate in the *Sample solution* (mg/mL)

**Acceptance criteria:** 50.0%–110.0%

• **Content of Edetate Disodium**

Perform this test if edetate disodium is a component in the Nasal Spray.

**Buffer:** 17 g/L of tetrabutylammonium hydrogen sulfate in water. Adjust with 2 M ammonium acetate to a pH of 4.4.

**Solution A:** Methanol, *Buffer*, and water (12:20:68)

**Solution B:** Methanol, *Buffer*, and water (70:7:23)

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 10 | 100 | 0 |
| 11 | 0 | 100 |
| 20 | 0 | 100 |

**Diluent:** Dissolve 250 mg of cupric sulfate in 400 mL of water. Add 100 mL of *Buffer*. Mix well and filter.

**Standard stock solution:** 0.25 mg/mL of USP Edetate Disodium RS in water

**Standard solution:** 0.05 mg/mL of USP Edetate Disodium RS in *Diluent* from *Standard stock solution*

**Sample solution:** Nominally 0.05 mg/mL of edetate disodium in *Diluent* prepared as follows. Prepare a composite by mixing NLT 5 containers of Nasal Spray in a suitable container. Transfer 5.0 mL of the composite solution to a 10-mL volumetric flask. Add 0.5 mL of 0.5 N hydrochloric acid. Dilute with *Diluent* to volume. Centrifuge for about 10 min at about 3600 rpm, and use the supernatant.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the percentage of the labeled amount of edetate disodium ($C_{10}H_{14}N_2O_8 \cdot 2H_2O \cdot 2Na$) in the portion of Nasal Spray taken:

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

$r_U$ = peak response of edetate disodium from the *Sample solution*

$r_S$ = peak response of edetate disodium from the *Standard solution*

$C_S$ = concentration of USP Edetate Disodium RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of edetate disodium in the *Sample solution* (mg/mL)

**Acceptance criteria:** 75.0%–110.0%

## PERFORMANCE TESTS

• **Delivered-Dose Uniformity** ⟨within container⟩

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

**Standard solution:** 3 µg/mL of USP Budesonide RS in acetonitrile

**Sample solution:** Nominally 3 µg/mL of budesonide in acetonitrile prepared as follows. Prime the metered spray by discharging a predetermined number of actuations to waste. Discharge the next selected actuation into a separate 10-mL volumetric flask for beginning and end-of-unit sample. [Note—Hold the 10-mL volumetric flask in an inverted position, and immediately turn upright after capturing the contents of the selected actuation.] Dilute with acetonitrile to volume.

Repeat this procedure with 9 additional units.

**Analysis**

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

Calculate the percentage of the labeled amount of budesonide ($C_{25}H_{34}O_6$) in each dose of Nasal Spray taken:

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

$r_U$ = peak response of budesonide from the *Sample solution*

$r_S$ = peak response of budesonide from the *Standard solution*

$C_S$ = concentration of USP Budesonide RS in the *Standard solution* (µg/mL)

$C_U$ = nominal concentration of budesonide in the *Sample solution* (µg/mL)

**Acceptance criteria**

**Tier 1**

1. The mean results of 10 dosage units at each beginning-of-unit sample and at end-of-unit sample are within 85.0%–115.0% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).
2. NMT 2 individual results outside of 80%–120% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).
3. None of the individual results outside of 75%–125% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).

If the criteria in *Tier 1* cannot be met, proceed to *Tier 2*.

**Tier 2:** Test an additional 20 units at each actuation. All the 60 results (including the results from *Tier 1*) meet the following *Acceptance criteria*.

1. The mean results of 30 units at each beginning-of-unit sample and at end-of-unit sample are within 85.0%–115.0% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).
2. NMT 6 of the 60 individual results outside of 80%–120% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).
3. None of the 60 individual results outside of 75%–125% of the labeled amount of budesonide ($C_{25}H_{34}O_6$).

• **Minimum Fill** ⟨755⟩**:** Meets the requirements

**IMPURITIES**

• **Organic Impurities**

**Buffer:** 2.7 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

**Solution A:** Acetonitrile and *Buffer* (27:73)

**Solution B:** Acetonitrile

**Mobile phase:** See *Table 2*.

**Table 2**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 30 | 100 | 0 |
| 50 | 92 | 8 |
| 60 | 85 | 15 |
| 75 | 85 | 15 |
| 75.1 | 100 | 0 |
| 80 | 100 | 0 |

**Diluent:** Acetonitrile and water (20:80)

**Calcium chloride solution:** 29 g/L of calcium chloride in water

[Note—Use low-actinic glassware for preparation of the *Standard solution* and *Sample solution*.]

**Standard stock solution:** 40 µg/mL of USP Budesonide RS in acetonitrile

**Standard solution:** 0.4 µg/mL of USP Budesonide RS in *Diluent* from *Standard stock solution*

**Sensitivity solution:** 0.1 µg/mL of USP Budesonide RS in *Diluent* from *Standard solution*

**Sample solution:** Nominally 100 µg/mL of budesonide prepared as follows. Prepare a composite by mixing NLT 5 containers of Nasal Spray in a suitable container. Transfer 4.0 mL of the well-stirred composite solution to a 10-mL volumetric flask. Add 0.5 mL of *Calcium chloride solution*. Mix and dilute with acetonitrile to volume. Transfer the solution into a centrifuge tube and centrifuge for about 10 min at about 3600 rpm. Pass the supernatant through a suitable syringe filter of 0.45-µm pore size into a test tube. Transfer 4.0 mL of the filtrate into a 10-mL volumetric flask and dilute with water to volume.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 240 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature:** 35°

**Flow rate:** 1.3 mL/min

**Injection volume:** 100 µL

**System suitability**

**Samples:** *Standard solution* and *Sensitivity solution*

[Note—See *Table 3* for the relative retention times. Budesonide, the active ingredient, elutes as two peaks for epimer A and epimer B under the chromatographic conditions.]

**Suitability requirements**

**Resolution:** NLT 1.5 between epimer B and epimer A, *Standard solution*

**Tailing factor:** NMT 2.0 for epimer B and epimer A of budesonide, *Standard solution*

**Relative standard deviation:** NMT 5.0% for the sum of epimer B and epimer A, *Standard solution*

**Signal-to-noise ratio:** NLT 10 for epimer B and epimer A, *Sensitivity solution*

**Analysis**

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

Calculate the percentage of budesonide glyoxal (epimers), budesonide acid, and any unspecified impurity in the portion of Nasal Spray taken:

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

$r_U$ = peak response of budesonide glyoxal (epimers), budesonide acid, or any unspecified impurity from the *Sample solution*

$r_S$ = sum of peak responses of budesonide epimer A and budesonide epimer B from the *Standard solution*

$C_S$ = concentration of USP Budesonide RS in the *Standard solution* (µg/mL)

$C_U$ = nominal concentration of budesonide in the *Sample solution* (µg/mL)

**Acceptance criteria:** See *Table 3*.

**Table 3**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| 16α-Hydroxyprednisolone[a,b] | 0.09 | — |
| Budesonide acetaldehyde acetal (epimers)[c,b] | 0.27, 0.28 | — |
| Budesonide D-homo analog[d,b] | 0.32 | — |
| Desonide[e,b] | 0.36 | — |
| Budesonide glyoxal (epimers)[f] | 0.64, 0.69 | 0.6[g] |
| Budesonide related compound E[h], budesonide pyruvic acid analog[i,j] | 0.83 | 1.0 |
| Budesonide related compound L[k,b] | 0.90 | — |
| Budesonide epimer B | 1.00 | — |
| Budesonide epimer A | 1.10 | — |
| Budesonide related compound G (epimers)[l,b] | 1.21, 1.29 | — |
| Budesonide 21-acetate (epimers)[m,b] | 2.12, 2.18 | — |
| Any unspecified impurity | — | 0.6 |
| Total impurities | — | 2.0 |

[a] 11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione.

[b] Process impurities, do not include in calculation of total impurities.

[c] 16α,17-[Ethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

[d] 16α,17-[Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione; also known as D-homobudesonide.

[e] 16α,17-[1-Methylethylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione.

[f] 16α,17-[Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al; also known as 21-dehydrobudesonide.

[g] Includes both epimers.

[h] Also known as 14,15-dehydrobudesonide or budesonide 14-ene.

[i] 16α,17-[Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-oic acid.

[j] When budesonide related compound E and budesonide pyruvic acid analog coelute, the result is reported as degradation product budesonide pyruvic acid analog.

[k] Also known as 11-ketobudesonide.

[l] Also known as 1,2-dihydrobudesonide.

[m] 16α,17-[Butylidenebis(oxy)]-11β-hydroxypregna-1,4-diene-3,20-dione-21-yl acetate.

**SPECIFIC TESTS**

• **pH** ⟨791⟩**:** 4.0–4.8

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial viable count does not exceed $10^2$ cfu/mL, and the total combined yeasts and molds count does not exceed $10^1$ cfu/mL. It meets the requirements of the tests for the absence of *Escherichia coli*, *Salmonella species*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

**ADDITIONAL REQUIREMENTS**

• **Packaging and Storage:** Store at controlled room temperature in an upright position, protected from light.

• **USP Reference Standards ⟨11⟩**
USP Budesonide RS
USP Edetate Disodium RS
USP Potassium Sorbate RS▲ (USP 1-Dec-2020)

**Auxiliary Information** - Please check for your question in the FAQs before contacting USP.

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| BUDESONIDE NASAL SPRAY | Documentary Standards Support | SM52020 Small Molecules 5 |

**Chromatographic Database Information:** Chromatographic Database

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