Triamcinolone Acetonide Nasal Spray

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Monographs Chemical Medicines Monographs 4 Expert Committee has revised the Triamcinolone Acetonide Nasal Spray monograph. The purpose for the revision is to increase the acceptance criteria in the test for *Organic Impurities* to accommodate FDA-approved drug products.

The specific changes are in *Table 4*:

- Triamcinolone acetonide ketoacid derivative from NMT 0.2% to NMT 0.3%
- Triamcinolone acetonide related compound C from NMT 2.0% to NMT 2.8%
- Total degradation products from NMT 2.5% to NMT 3.4%

The Triamcinolone Acetonide Nasal Spray Revision Bulletin replaces the version that is scheduled to become official on May 1, 2019. Please note that *General Notices, 3.10 Applicability of Standards* discusses early adoption. For questions regarding compliance, please consult your relevant regulatory authority.

Should you have any questions, please contact Nicholas Garito, Scientific Liaison (301-816-8321 or njg@usp.org).

Triamcinolone Acetonide Nasal Spray

DEFINITION

Triamcinolone Acetonide Nasal Spray is an aqueous suspension of Triamcinolone Acetonide. It is supplied in a form suitable for nasal administration. It contains NLT 90.0% and NMT 110.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).

IDENTIFICATION

• **A.** 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**

Buffer A: 3.4 g/L of monobasic potassium phosphate prepared as follows. Dissolve 3.4 g of monobasic potassium phosphate in 900 mL of water, adjust with 5 M sodium hydroxide to a pH of 7.0, and dilute with water to 1000 mL.

Buffer B: 3.4 g/L of monobasic potassium phosphate prepared as follows. Dissolve 3.4 g of monobasic potassium phosphate in 900 mL of water, adjust with phosphoric acid to a pH of 3.0, and dilute with water to 1000 mL.

Solution A: Acetonitrile and *Buffer A* (27.5: 72.5)

Solution B: Acetonitrile and *Buffer A* (60:40)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	60	40
30.1	0	100
44	0	100
44.1	100	0
52	100	0

Diluent: Acetonitrile and *Buffer B* (27.5: 72.5)

Standard stock solution: 0.4 mg/mL of USP Triamcinolone Acetonide RS in acetonitrile. Sonication for 15 min may be used to aid in dissolution.

Standard solution: 40 µg/mL of USP Triamcinolone Acetonide RS from *Standard stock solution* in *Diluent*

System suitability stock solution: 0.04 mg/mL of USP Triamcinolone Acetonide Related Compound B RS and USP Triamcinolone Acetonide Related Compound C RS in *Diluent*

System suitability solution: 40 µg/mL of USP Triamcinolone Acetonide RS and 0.8 µg/mL each of USP Triamcinolone Acetonide Related Compound B RS and USP Triamcinolone Acetonide Related Compound C RS in suitable volumes of *Standard stock solution* and *System suitability stock solution* in *Diluent*

Sample solution: Nominally 40 µg/mL of triamcinolone acetonide prepared as follows. Transfer a portion of the Nasal Spray, equivalent to 4 mg of triamcinolone acetonide, to a 100-mL volumetric flask. Dissolve in 28 mL of acetonitrile with the aid of sonication. Allow to cool to room temperature and dilute with *Buffer B* to volume. Centrifuge and use the clear supernatant.

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: 0.75 mL/min

Injection volume: 100 µL

System suitability

Samples: *Standard solution* and *System suitability solution*
[NOTE—See *Table 4* for the relative retention times.]

Suitability requirements

Resolution: NLT 3.0 between triamcinolone acetonide related compound C and triamcinolone acetonide related compound B; NLT 3.0 between triamcinolone acetonide related compound B and triamcinolone acetonide, *System suitability solution*

Tailing factor: NMT 1.3 for triamcinolone acetonide, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$) in the portion of Nasal Spray taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Triamcinolone Acetonide RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of triamcinolone acetonide in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

• **CONTENT OF EDETATE DISODIUM**

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

Buffer: Add 990 mL of water into a 1000-mL beaker, followed by 10.0 mL of 1.0 M tetrabutylammonium hydroxide in methanol. Adjust with phosphoric acid to a pH of 7.0.

Mobile phase: Acetonitrile and *Buffer* (15:85)

Solution A: 40 g/L of sodium chloride and 2 g/L of sodium acetate. Adjust with glacial acetic acid to a pH of 5.5.

Solution B: 1.0 g/L of cupric sulfate in water

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 0.5 mg/mL of edetate disodium in water. Sonication may be used to aid in dissolution.

Standard solution: 0.05 mg/mL of edetate disodium. Transfer 5.0 mL of *Standard stock solution* to a 50-mL volumetric flask. Next add 10 mL of *Solution A* and then add 5.0 mL of acetonitrile. Mix the resulting solution and then add 20.0 mL of *Solution B*, dilute with *Diluent* to volume, and mix.

Sample solution: Combine the contents of NLT 5 bottles of Nasal Spray and mix the contents to obtain a composite suspension. Transfer a 5.0-g portion of the Nasal Spray to a 50-mL volumetric flask. Add 10 mL of *Solution A* and 5.0 mL of acetonitrile. Mix and sonicate for 10 min and allow the solution to equilibrate to room temperature. Add 20.0 mL of *Solution B*, and sonicate for 10 min. Allow the sample to equilibrate to room temperature and dilute with *Diluent* to volume. Centrifuge a portion for 15 min, and use the supernatant. [NOTE—Centrifuging at 4000 rpm for 15 min may be suitable.]

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

Mode: LC
Detector: UV 265 nm
Column: 4.1-mm × 15-cm; 5-µm packing L21
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 edetate disodium ($C_{10}H_{14}N_2Na_2O_8$) in the portion of Nasal Spray taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of edetate disodium in the *Standard solution* (mg/mL)
V = volume of the *Sample solution* (mL)
W = weight of Nasal Spray in the *Sample solution* (mg)

Acceptance criteria: 0.045%–0.055%

Change to read:

• **CONTENT OF BENZALKONIUM CHLORIDE**

Perform this test if benzalkonium chloride is a known component in the Nasal Spray.
Buffer: Dissolve 10.8 g of monobasic sodium phosphate dihydrate in 90 mL of water, and adjust with phosphoric acid a pH of 2.5. Dilute with water to 100 mL.
Solution A: Mix 50 mL of *Buffer*, 750 mL of water, and 200 mL of methanol. Add 5 mL of triethylamine. Mix and adjust with phosphoric acid to a pH of 2.5.
Solution B: Methanol and phosphoric acid prepared as follows. Mix 1 L of methanol with 50 mL of phosphoric acid.
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	55	45
3.0	5	95
3.2	55	45
5.0	55	45

Diluent: 1% (v/v) hydrochloric acid in methanol
System suitability solution: ▲0.04 mg/mL of USP Benzalkonium Chloride RS in *Diluent* prepared as follows. Transfer a suitable volume of USP Benzalkonium Chloride RS to a suitable volumetric flask and dilute with *Diluent* to volume.▲ USP 1-May-2019
Standard stock solution: 0.2 mg/mL of USP Benzalkonium Bromide RS in water. [NOTE—A few drops of methanol may be used to resolve the formation of foam prior to dilution.]
Standard solution: 0.04 mg/mL of USP Benzalkonium Bromide RS. Transfer an aliquot of *Standard stock solution* to a suitable volumetric flask, and add water equal to 30% of the flask volume. Dilute with *Diluent* to volume.
Sample solution: Combine the contents of NLT 5 bottles of Nasal Spray and mix the contents to obtain a composite suspension. Transfer a 5.0-g portion of the Nasal Spray to a 10-mL volumetric flask. Dilute with *Diluent* to volume. Centrifuge and use the supernatant. [NOTE—Centrifuging at 4000 rpm for 15 min may be suitable. Supernatant may be passed through a suitable filter of NMT 0.2-µm pore size.]
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 3.0-cm; 2.6-µm packing L1
Column temperature: 50°
Flow rate: 2 mL/min
Injection volume: 100 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 3* for the relative retention times. The peak due to the C10 analog may not be visible due to its low concentration in the *System suitability solution*. ▲The *Standard solution* may contain only one peak as it is predominantly the C12 analog.]▲ USP 1-May-2019
Suitability requirements
Resolution: NLT 2.5 between the pairs of C12 and C14 homologs and C14 and C16 homologs of benzalkonium, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 2%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the sum of each corrected benzalkonium peak response (r_U) as follows:

$$\text{Result} = \Sigma(r_U) \times (1/F)$$

r_U = peak response of each benzalkonium homolog from the *Sample solution*
F = relative response factor of the corresponding benzalkonium homolog relative to benzalkonium bromide (see *Table 3*)

Table 3

Benzalkonium Chloride Analog	Relative Retention Time	Relative Response Factor
C10	0.65	1.3
C12	1.0	1.2
C14	1.35	1.0
C16	1.59	0.98

Calculate the percentage of benzalkonium chloride in the portion of Nasal Spray taken:

$$\text{Result} = (\Sigma r_U/r_S) \times C_S \times (V/W) \times 100$$

Σr_U = sum of the corrected peak responses of the benzalkonium homologs from the *Sample solution*
r_S = peak response of benzalkonium from the *Standard solution*
C_S = concentration of USP Benzalkonium Bromide RS in the *Standard solution* (mg/mL)
V = volume of the *Sample solution* (mL)
W = weight of Nasal Spray in the *Sample solution* (mg)

Acceptance criteria: 0.0135%–0.0165%

PERFORMANCE TESTS

Change to read:

• **DELIVERED DOSE UNIFORMITY (BETWEEN CONTAINERS)**
Buffer: 7.0 g/L of sodium perchlorate prepared as follows. Dissolve 7.0 g of sodium perchlorate in 900 mL of water, adjust with perchloric acid to a pH of 3.0, and dilute with water to 1000 mL.
Mobile phase: Acetonitrile and *Buffer* (50:50)
Standard solution: 40 µg/mL of USP Triamcinolone Acetonide RS in *Mobile phase*
Sample solution: Nominally 40 µg/mL of triamcinolone acetonide prepared as follows. Transfer a portion of Nasal Spray, equivalent to 4.0 mg of triamcinolone acetonide, to a suitable volumetric flask. Add *Mobile phase* to 80% of the flask volume. Sonicate for 15 min. Allow to equilibrate to room temperature. Dilute with *Mobile phase* to volume. Centrifuge and pass the supernatant through a filter of 0.45-µm pore size. [NOTE—Centrifuging at 4000 rpm for 45 min may be suitable.]
Repeat this procedure with 9 additional ▲containers.▲ USP 1-May-2019
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 40 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 2%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ▲the labeled amount of▲ USP 1-May-2019 triamcinolone acetonide ($C_{24}H_{31}FO_6$) in the portion of Nasal Spray taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Triamcinolone Acetonide RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of triamcinolone acetonide in the *Sample solution* (µg/mL)

Acceptance criteria
Tier 1: The content of each of the 10 ▲containers▲ USP 1-May-2019 is within 90.0%–110.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$). If the criterion in *Tier 1* cannot be met, proceed to *Tier 2*.
Tier 2: If the content of 1 ▲container▲ USP 1-May-2019 is outside 90.0%–110.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$) and the content of none of the ▲containers▲ USP 1-May-2019 is outside 85.0%–115.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$), test an additional 20 ▲containers.▲ USP 1-May-2019 All the 30 results (including the results from *Tier 1*) meet the following acceptance criteria.
1. The content of each of 29 out of 30 ▲containers▲ USP 1-May-2019 is within 90.0%–110.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
2. The content of each of the 30 ▲containers▲ USP 1-May-2019 is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).

Change to read:

• **DELIVERED DOSE UNIFORMITY (WITHIN CONTAINER)**
Buffer: 7.0 g/L of sodium perchlorate prepared as follows. Dissolve 7.0 g of sodium perchlorate in 900 mL of water, adjust with perchloric acid to a pH of 3.0, and dilute with water to 1000 mL.
Mobile phase: Acetonitrile and *Buffer* ▲(50:50)▲ USP 1-May-2019
Standard solution: 4.8 µg/mL of USP Triamcinolone Acetonide RS in *Mobile phase*
Beginning sample solution (BOU): Hold the pump upright, actuate 5 times, and wipe the nosepiece dry. Hold a 25-mL volumetric flask in an inverted position and actuate the pump. Quickly turn the flask upright, wait 10 s, and repeat the process. Add 15 mL of *Mobile phase* while rinsing the neck of the flask and sonicate for 15 min. Allow the flask to equilibrate to room temperature, and dilute with *Mobile phase* to volume. Centrifuge and use the clear supernatant. [NOTE—Centrifuging at 4000 rpm for 15 min may be suitable.]
Middle sample solution (MOU): Using the same pump as above, discharge an appropriate number of actuations to arrive at 50% of the labeled number of actuations to waste and wipe the nosepiece dry. Hold a 25-mL volumetric flask in an inverted position and actuate the pump to collect the next actuation. Quickly turn the flask upright, wait 10 s, and repeat the process to collect the next actuation. Add 15 mL of *Mobile phase* while rinsing the neck of the flask and sonicate for 15 min. Allow the flask to equilibrate to room temperature, and dilute with *Mobile phase* to volume. Centrifuge and use the clear supernatant. This is the MOU sample. [NOTE—Centrifuging at 4000 rpm for 15 min may be suitable.]
End sample solution (EOU): Using the same pump as above, discharge the next appropriate number of actuations to arrive at 100% of the labeled number of actuations to waste, and wipe the nosepiece dry. Hold a 25-mL volumetric flask in an inverted position and actuate the pump to collect the next actuation. Quickly turn the flask upright, wait 10 s, and repeat the process to collect the next actuation. Add 15 mL of *Mobile phase* while rinsing the neck of the flask and sonicate for 15 min. Allow the flask to equilibrate to room temperature, and dilute with *Mobile phase* to volume. Centrifuge and use the clear supernatant. This is the EOU sample. [NOTE—Centrifuging at 4000 rpm for 15 min may be suitable.]
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 200 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution*, *Beginning sample solution*, *Middle sample solution*, and *End sample solution*
Calculate the percentage of the labeled amount of the triamcinolone acetonide ($C_{24}H_{31}FO_6$) delivered dose:

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

r_U = peak response from the appropriate *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Triamcinolone Acetonide RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of triamcinolone acetonide in the appropriate *Sample solution* (µg/mL)

Acceptance criteria
Calculate the mean delivered dose from the BOU results from all 10 containers.
Calculate the mean delivered dose from the MOU results from all 10 containers.
Calculate the mean delivered dose from the EOU results from all 10 containers.
Calculate the ▲container delivery mean▲ USP 1-May-2019 from the BOU, MOU, and EOU results from each of the 10 containers.
Tier 1
1. Mean delivered dose of BOU samples from all 10 ▲containers▲ USP 1-May-2019 is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
2. Mean delivered dose of MOU samples from all 10 ▲containers▲ USP 1-May-2019 is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
3. Mean delivered dose of EOU samples from all 10 ▲containers▲ USP 1-May-2019 is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
4. NMT 1 ▲container delivery mean from the 10 containers▲ USP 1-May-2019 is outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
5. None of the ▲container delivery means from the 10 containers▲ USP 1-May-2019 is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).

▲*Tier 1* criteria 1–3 must be met. If criterion 4 or 5 cannot be met, proceed to *Tier 2*.▲ USP 1-May-2019

Tier 2: ▲If NMT 3 container delivery means are outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$) and none of the container delivery means is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$), test an additional 20 containers. All 30 container delivery means (including the results from *Tier 1*) meet the following acceptance criteria.▲ USP 1-May-2019
1. NMT 3 of 30 ▲container delivery means▲ USP 1-May-2019 are outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).
2. None of the 30 ▲container delivery means▲ USP 1-May-2019 is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide ($C_{24}H_{31}FO_6$).

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**
Buffer A, Buffer B, Solution A, Solution B, Mobile phase, Diluent, Standard solution, System suitability solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Sample: *Sample solution*
Calculate the percentage of each degradation product in the portion of Nasal Spray taken:

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

r_I = peak response of each degradation product from the *Sample solution*
r_U = peak response of triamcinolone acetonide from the *Sample solution*

Acceptance criteria: See *Table 4*. Disregard any peak below 0.05%.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Triamcinolone acetonide ketoacid derivative[a]	0.4	▲0.3▲ (RB 1-May-2019)
Triamcinolone acetonide related compound C	0.83	▲2.8▲ (RB 1-May-2019)
Triamcinolone acetonide related compound B	0.91	0.4
Triamcinolone acetonide	1.0	—
Any other individual degradation product	—	0.1
Total degradation products	—	▲3.4▲ (RB 1-May-2019)

[a] 9-Fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-(11β,16α)-3,20-dioxopregna-1,4-diene-21-oic acid.

SPECIFIC TESTS

• **pH** ⟨791⟩**:** 4.5–6.0

Delete the following:

▲• **OSMOLALITY AND OSMOLARITY** ⟨785⟩**:** 280–380 mOsmol/kg▲ USP 1-May-2019
• **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 is NMT 10^1 cfu/mL and the total combined molds and yeasts count is NMT 10^1 cfu/mL.
• **PARTICLE SIZE**
Analysis: Shake the Nasal Spray and prime the pump by spraying 3–4 times. Actuate the spray and collect the sample on a glass microscope slide held above the nozzle, and repeat to prepare a second slide. Using light microscopy, determine the dimension of NLT 200 particles of triamcinolone acetonide by measuring NLT 100 particles from 20 random fields of view for each slide prepared. Repeat the procedure using a second container of Nasal Spray.
Acceptance criteria: See *Table 5*.

Table 5

Particle Size (µm)	Acceptance Criteria (%)
<1	NMT 3
1–6	70–95
>9	NMT 4

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in a tight, light-resistant container, and store at controlled room temperature.

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Benzalkonium Bromide RS
  USP Benzalkonium Chloride RS
  USP Triamcinolone Acetonide RS
  USP Triamcinolone Acetonide Related Compound B RS
  9-Fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene) bis(oxy)]-(11β,16α)-pregna-1,4,14-triene-3,20-dione.
  $C_{24}H_{29}FO_6$ 432.48
  USP Triamcinolone Acetonide Related Compound C RS
  9-Fluoro-11,21,21-trihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-(11β,16α)-pregna-1,4-diene-3,20-dione.
  $C_{24}H_{31}FO_7$ 450.50