Triamcinolone Acetonide Nasal Spray

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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 (C₂₄H₃₁FO₆).

**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 B (60:40)
  - **Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>30.1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>44</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>44.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>52</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Chromatographic system**
  - **Mode:** LC

- **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 (C₂₄H₃₁FO₆) in the portion of Nasal Spray taken:
    \[
    \text{Result} = \left( \frac{r_S}{r_U} \right) \times \left( \frac{C_U}{C_S} \right) \times 100
    \]
    - \( r_U \) = 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 EDTATE 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 solution to equilibrate to room temperature and dilute with Diluent to volume. Centrifuge a portion for 15 min, and use the supernatant.
- **Chromatographic system**
  - (See Chromatography (621), System Suitability.)

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**2 Triamcinolone**

**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 to 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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>3.0</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>3.2</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>5.0</td>
<td>55</td>
<td>45</td>
</tr>
</tbody>
</table>

**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. **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

<table>
<thead>
<tr>
<th>Benzalkonium Chloride Analog</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10</td>
<td>0.65</td>
<td>1.3</td>
</tr>
<tr>
<td>C12</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>C14</td>
<td>1.35</td>
<td>1.0</td>
</tr>
<tr>
<td>C16</td>
<td>1.59</td>
<td>0.98</td>
</tr>
</tbody>
</table>

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

\[
\text{Result} = \left( \frac{\Sigma r_U}{r_S} \times C_T \times \frac{V}{W} \right) \times 100
\]

\[
\Sigma r_U = \text{sum of the corrected peak responses of the benzalkonium homologs from the Sample solution}
\]

\[
r_S = \text{peak response of benzalkonium from the Standard solution}
\]

\[
C_T = \text{concentration of USP Benzalkonium Bromide RS in the Standard solution (mg/mL)}
\]

\[
V = \text{volume of the Sample solution (mL)}
\]

\[
W = \text{weight of Nasal Spray in the Sample solution (mg)}
\]

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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. (See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm x 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 Triamcinolone Acetonide (C₂₄H₃₁F₄O₆) in the portion of Nasal Spray taken:

Result = \( \frac{r_f}{r_s} \times \left( \frac{C_s}{C_U} \right) \times 100 \)

where:

- \( r_f \): 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 is within 90.0%–110.0% of the labeled amount of triamcinolone acetonide (C₂₄H₃₁F₄O₆).

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

**Tier 2:** If the content of 1 container is outside 90.0%–110.0% of the labeled amount of triamcinolone acetonide (C₂₄H₃₁F₄O₆) and the content of none of the 9 containers is outside 85.0%–115.0% of the labeled amount of triamcinolone acetonide (C₂₄H₃₁F₄O₆), test an additional 20 containers. 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 is within 90.0%–110.0% of the labeled amount of triamcinolone acetonide (C₂₄H₃₁F₄O₆).

2. The content of each of the 30 containers is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide (C₂₄H₃₁F₄O₆).

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)

Standard solution: 4.8 µg/mL of USP Triamcinolone Acetonide RS in Mobile phase

Beginning sample solution (BOU): Hold the pump upright, actuate 3 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.

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. 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.

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.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm x 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%
4 Triamcinolone

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 (C₂₃H₃₁FO₈) delivered dose:

\[
\text{Result} = \left( \frac{r_s}{r_u} \right) \times \left( \frac{C_i}{C_u} \right) \times 100
\]

- \( r_u \) = peak response from the appropriate Sample solution
- \( r_s \) = peak response from the Standard solution
- \( C_i \) = 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 MOU results from all 10 containers.
Calculate the mean delivered dose from the EOU results from all 10 containers.

* Tier 1

1. Mean delivered dose of MOU samples from all 10 containers\(^\text{USP 1-May-2019}^\) is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).
2. Mean delivered dose of EOU samples from all 10 containers\(^\text{USP 1-May-2019}^\) is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).
3. Mean delivered dose of EOU samples from all 10 containers\(^\text{USP 1-May-2019}^\) is within 85.0%–115.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).
4. NMT 1 container delivery mean\(^\text{USP 1-May-2019}^\) from the 10 containers\(^\text{USP 1-May-2019}^\) is outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).
5. None of the container delivery means from the 10 containers\(^\text{USP 1-May-2019}^\) is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).

* Tier 1 criteria 1–3 must be met. If criterion 4 or 5 cannot be met, proceed to Tier 2.\(^\text{USP 1-May-2019}^\)

* Tier 2

If NMT 3 container delivery means are outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈) and none of the container delivery means is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈), test an additional 20 containers. All 30 container delivery means (including the results from Tier 1) meet the following acceptance criteria.\(^\text{USP 1-May-2019}^\)

1. NMT 3 of 30 container delivery means\(^\text{USP 1-May-2019}^\) are outside 80.0%–120.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).
2. None of the 30 container delivery means\(^\text{USP 1-May-2019}^\) is outside 75.0%–125.0% of the labeled amount of triamcinolone acetonide (C₂₃H₃₁FO₈).

**IMPURIES**

**Change to read:**

- **Organic Impurities**

**Specific Tests**

- **pH (791):** 4.5–6.0

Delete the following:

- **Osmolality and Osmolarity (785):** 280–380 mOsmol/kg
- **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 10¹ cfu/mL and the total combined molds and yeasts count is NMT 10¹ 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

<table>
<thead>
<tr>
<th>Particle Size (µm)</th>
<th>Acceptance Criteria (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>NMT 3</td>
</tr>
<tr>
<td>1–6</td>
<td>70–95</td>
</tr>
<tr>
<td>&gt;9</td>
<td>NMT 4</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in a tight, light-resistant container, and store at controlled room temperature.

**USP Reference Standards**

- 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-methylethyldene)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-methylethyldene)bis(oxy)]-(11β,16α)-pregna-1,4-diene-3,20-dione. C_{24}H_{31}FO_7 450.50