Cisatracurium Besylate

C₆₅H₈₂N₂O₁₈S₂ 1243.48
Isoquinolinium, 2,2′-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]bis[1-{[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium dibenzenesulfonate, [1R-[1α,2α(1′R*,2′R*)]; (1R,2R)-2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate, pentamethylenes ester [96946-42-8].

DEFINITION
Cisatracurium Besylate contains NLT 97.0% and NMT 102.0% of cisatracurium besylate (C₆₅H₈₂N₂O₁₈S₂), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION
• A. INFRARED ABSORPTION (197K)
• 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
Buffer: 33.3 g/L of ammonium formate prepared as follows. Dissolve 32.8 g of ammonium formate in 984 mL of water, and add 16 mL of anhydrous formic acid.
Mobile phase: Acetonitrile, methanol, and Buffer (20:20:60)
Diluent: Acetonitrile, methanol, and water (20:20:60). Add 0.4 mL of anhydrous formic acid per L.
System suitability solution: 0.7 mg/mL of USP Cisatracurium Besylate System Suitability Mixture RS in Diluent
Standard solution: 0.7 mg/mL of USP Cisatracurium Besylate RS in Diluent
Sample solution: 0.7 mg/mL of Cisatracurium Besylate in Diluent
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 25.0-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 20 µL
Run time: NLT 2.5 times the retention time of cisatracurium

System suitability
Samples: System suitability solution and Standard solution
[NOTE—See Table 1 for relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between the peaks for R-cis-R′-trans-atracurium and cisatracurium, System suitability solution
Tailing factor: NMT 1.7 for cisatracurium, System suitability solution
Relative standard deviation: NMT 1.5%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of cisatracurium besylate (C₆₅H₈₂N₂O₁₈S₂) in the portion of Cisatracurium Besylate taken:

Result = \( \frac{r_U}{r_T} \times \frac{C_S}{C_U} \times 100 \)

Where:
- \( r_U \) = peak response from the Sample solution
- \( r_T \) = sum of all the peak responses from the Sample solution
- \( C_S \) = concentration of USP Cisatracurium Besylate RS in the Standard solution (mg/mL)
- \( C_U \) = concentration of Cisatracurium Besylate in the Sample solution (mg/mL)

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis.

IMPURITIES
• Residue on Ignition (281): NMT 0.1%

Change to read:

• Organic impurities
Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Analysis
Sample: Sample solution
Calculate the percentage of each impurity in the portion of Cisatracurium Besylate taken:

Result = \( \frac{r_U}{r_T} \times 100 \)

Where:
- \( r_U \) = peak response of each impurity in the Sample solution
- \( r_T \) = sum of all the peak responses from the Sample solution

Acceptance criteria: See Table 1. Disregard any peak representing less than 0.09% of the area of the major peak.
Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzensulfonic acid</td>
<td>0.10</td>
<td>—</td>
</tr>
<tr>
<td>cis-Quaternary acid</td>
<td>0.14</td>
<td>0.2</td>
</tr>
<tr>
<td>(8)-N-Methylaudanosine</td>
<td>0.16</td>
<td>0.2</td>
</tr>
<tr>
<td>(8)-Laudanosine</td>
<td>0.20</td>
<td>0.6</td>
</tr>
<tr>
<td>cis-Quaternary methyl ester</td>
<td>0.23</td>
<td>0.4</td>
</tr>
<tr>
<td>cis-Quaternary alcohol</td>
<td>0.29</td>
<td>0.5</td>
</tr>
<tr>
<td>R-trans-R'-trans-Atracurium</td>
<td>0.74</td>
<td>0.2</td>
</tr>
<tr>
<td>R-cis-R'-trans-Atracurium</td>
<td>0.87</td>
<td>0.8</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>trans-Monoquaternary compound</td>
<td>1.17</td>
<td>0.5</td>
</tr>
<tr>
<td>trans-Monoacrylate</td>
<td>1.28</td>
<td>0.5</td>
</tr>
<tr>
<td>cis-Monoquaternary compound</td>
<td>1.39</td>
<td>0.7</td>
</tr>
<tr>
<td>cis-cis-Friester analog</td>
<td>1.46</td>
<td>0.4</td>
</tr>
<tr>
<td>cis-Monoacrylate</td>
<td>1.56</td>
<td>1.0</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

This peak is due to the counterion and is not to be reported or included in total impurities.

<table>
<thead>
<tr>
<th>Sample solution:</th>
<th>Standard solution and Sample solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium</td>
<td>Will be calculated based on the concentration of methyl benzenesulfonate and methyl p-toluene sulfonate in the portion of Cisatracurium Besylate taken.</td>
</tr>
</tbody>
</table>

### SPECIFIC TESTS

- **Limit of Methyl Benzenesulfonate**
  - Methyl benzenesulfonate is slowly hydrolyzed in aqueous solution. Prepare the solutions immediately before use.

### Procedure

- **Standard solution A**: 1.2 mg/mL of methyl benzenesulfonate in acetonitrile
- **Standard solution B**: 48 µg/mL of methyl benzenesulfonate from Standard stock solution A in acetonitrile

### Sample solution

Nominally 0.2 g/mL of Cisatracurium Besylate in Mobile phase is prepared as follows. Transfer 1.0 g of Cisatracurium Besylate into a suitable separatory funnel. Immediately add 25 µL of Internal standard solution, and dissolve the contents in 25 mL of water using vigorous shaking. Add 25 mL of ethyl acetate, and shake vigorously for 2 min. Allow the phases to separate until the aqueous layer is clear and for NMT 2 h. Evaporate the organic layer to dryness in a current of air. Dissolve the residue in 5.0 mL of Mobile phase by sonication and gentle swirling.

### Chromatographic system

**Mode:** LC
**Detector:** UV 214 nm
**Column:** 4.6-mm × 25.0-cm; 5-µm packing L1
**Flow rate:** 1 mL/min
**Injection volume:** 20 µL
**Run time:** 5 times the retention time of methyl benzenesulfonate

### System suitability

- **Sample:** Standard solution
- **Suitability requirements**
  - Resolution: NLT 2.0 for methyl benzenesulfonate and methyl p-toluene sulfonate

### Analysis

**Samples:** Standard solution and Sample solution

Calculate the concentration of methyl benzenesulfonate in the portion of Cisatracurium Besylate taken:

\[ \text{Result} = \left( \frac{R_s}{R_U} \right) \times \left( \frac{C_s}{C_U} \right) \]

- \( R_s \) = peak height ratio of methyl benzenesulfonate to the internal standard from the Sample solution
- \( R_U \) = peak height ratio of methyl benzenesulfonate to the internal standard from the Standard solution
- \( C_s \) = concentration of methyl benzenesulfonate in the Standard solution (µg/mL)
- \( C_U \) = nominal concentration of Cisatracurium Besylate in the Sample solution (g/mL)

### Acceptance criteria
- NMT 10 ppm

### Optical Rotation (7815)

- **Procedures, Specific Rotation**
  - Sample solution: 10.0 mg/mL in acetonitrile

- **Acceptance criteria:** −60.0° to −54.0° at 20°, calculated on the anhydrous and solvent-free basis

### Water Determination (921)

- **Sample solution:** 7 mg/mL of Cisatracurium Besylate in water

- **Acceptance criteria:** 5.0–6.5

### Change to read:

- **PH (791)**
  - Sample solution: 7 mg/mL of Cisatracurium Besylate in water

- **Acceptance criteria:** 5.0–6.5

### Packaging and Storage

- **Preserve in tight, light-resistant containers. Store cold, desiccated.

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Change to read:

- **USP Reference Standards** (11)
  - USP Cisatracurium Besylate RS
  - USP Cisatracurium Besylate System Suitability Mixture RS
  - Cisatracurium besylate.
  - R-trans-R'-trans-Atracurium · besylate: (IRA 1-Jul-2016)

(1R,1'R,2R,2'S)-2,2'-(3,11-Dioxo-4,10-dioxa-
-tridecamethylene)bis(1,2,3,4-tetrahydro-6,7-
dimethoxy-2-methyl-1-veratrylisoquinolinium)
dibenzenesulfonate.

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-tridecamethylene)bis(1,2,3,4-tetrahydro-6,7-
dimethoxy-2-methyl-1-veratrylisoquinolinium)
dibenzenesulfonate.
C₆₅H₈₂N₂O₁₈S₂  1243.48
Other related compounds.