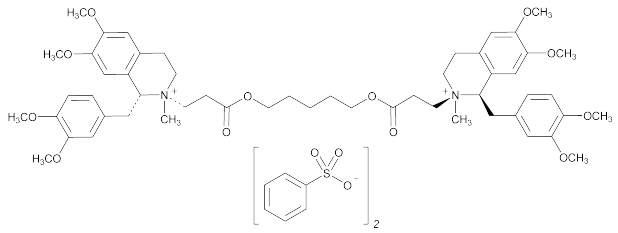
# Cisatracurium Besylate



$C_{65}H_{82}N_2O_{18}S_2$ 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-, dibenzenesulfonate, [1*R*-[1α,2α(1′*R**,2′*R**)]]-;
(1*R*,2*R*)-2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate, pentamethylene ester [96946-42-8].

## DEFINITION

Cisatracurium Besylate contains NLT 97.0% and NMT 102.0% of cisatracurium besylate ($C_{65}H_{82}N_2O_{18}S_2$), 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 1 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 ($C_{65}H_{82}N_2O_{18}S_2$) in the portion of Cisatracurium Besylate 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 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:

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

$r_U$ = peak response of each impurity from 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**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| ●Benzenesulfonic acid● (IRA 1-Jul-2016)[a] | 0.10 | — |
| *cis*-Quaternary acid[b] | 0.14 | 0.2 |
| (*R*)-*N*-Methyllaudanosine[c] | 0.16 | 0.2 |
| (*R*)-Laudanosine[d] | 0.20 | 0.6 |
| *cis*-Quaternary methyl ester[e] | 0.23 | 0.4 |
| *cis*-Quaternary alcohol[f] | 0.29 | 0.5 |
| *R-trans-R′-trans*-Atracurium[g] | 0.74 | 0.2 |
| *R-cis-R′-trans*-Atracurium[h] | 0.87 | 0.8 |
| Cisatracurium | 1.0 | — |
| *trans*-Monoquaternary compound[i] | 1.17 | 0.5 |
| *trans*-Monoacrylate[j] | 1.28 | 0.5 |
| *cis*-Monoquaternary compound[k] | 1.39 | 0.7 |
| *cis-cis*-Triester analog[l] | 1.46 | 0.4 |
| *cis*-Monoacrylate[m] | 1.56 | 1.0 |
| Any individual unspecified impurity | — | 0.1 |
| Total impurities | — | 3.0 |

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

[b] (1*R*,2*R*)-2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium. ● (IRA 1-Jul-2016)

[c] (*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2,2-dimethyl-1-veratrylisoquinolinium. ● (IRA 1-Jul-2016)

[d] (*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinoline.

[e] (1*R*,2*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[2-(methoxycarbonyl)ethyl]-2-methyl-1-veratrylisoquinolinium. ● (IRA 1-Jul-2016)

[f] (1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(9-hydroxy-3-oxo-4-oxanonyl)-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium. ● (IRA 1-Jul-2016)

[g] (1*R*,1′*R*,2*S*,2′*S*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[h] (1*R*,1′*R*,2*R*,2′*S*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[i] (1*R*,1′*R*,2*S*)-2-Methyl-2,2′-(3,11-dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[j] (1*R*,2*S*)-2-(3,11-Dioxo-4,10-dioxa-12-tridecenyl)-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[k] (1*R*,1′*R*,2*R*)-2-Methyl-2,2′-(3,11-dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[l] (1*R*,1′*R*,2*R*,2′*R*)-2,2′-(3,7,15-Trioxo-4,8,14-trioxaheptadecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

[m] (1*R*,2*R*)-2-(3,11-Dioxo-4,10-dioxa-12-tridecenyl)-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium). ● (IRA 1-Jul-2016)

- **LIMIT OF METHYL BENZENESULFONATE**

[NOTE—Prepare the solutions immediately before use. Methyl benzenesulfonate is slowly hydrolyzed in aqueous solutions.]

**Mobile phase:** Acetonitrile and water (45:55)

**Internal standard solution:** 1.2 mg/mL of methyl *p*-toluenesulfonate in acetonitrile

**Standard stock solution A:** 1.2 mg/mL of methyl benzenesulfonate in acetonitrile

**Standard stock solution B:** 48 µg/mL of methyl benzenesulfonate from *Standard stock solution A* in *Mobile phase* prepared as follows. Transfer 2.0 mL of *Standard stock solution A* and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

**Standard solution:** 2.4 µg/mL of methyl benzenesulfonate from *Standard stock solution B* in *Mobile phase*

**Sample solution:** Nominally 0.2 g/mL of Cisatracurium Besylate in *Mobile phase* prepared as follows. Transfer 1.0 g of Cisatracurium Besylate into a suitable separator. 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**
(See *Chromatography* ⟨621⟩*, System Suitability*.)
**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 3.0 between methyl benzenesulfonate and methyl *p*-toluenesulfonate
**Relative standard deviation:** NMT 2.0% for methyl benzenesulfonate and methyl *p*-toluenesulfonate

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the concentration of methyl benzenesulfonate in the portion of Cisatracurium Besylate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U)$$

$R_U$ = peak height ratio of methyl benzenesulfonate to the internal standard from the *Sample solution*
$R_S$ = 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

## SPECIFIC TESTS

- **OPTICAL ROTATION** ⟨**781S**⟩**,** *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

***Delete the following:***

●● **pH** ⟨**791**⟩
**Sample solution:** 7 mg/mL of Cisatracurium Besylate in water
**Acceptance criteria:** 5.0–6.5● (IRA 1-Jul-2016)

***Change to read:***

- **WATER DETERMINATION** ⟨**921**⟩●● (IRA 1-Jul-2016)**:** NMT 5.0%. ● [NOTE—*Method Ia* or *Method Ic* may be used.]● (IRA 1-Jul-2016)

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store cold, desiccated.

***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)
  (1*R*,1′*R*,2*S*,2′*S*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.
  $C_{65}H_{82}N_2O_{18}S_2$ 1243.48
  *R-cis-R′-trans*-Atracurium •besylate:• (IRA 1-Jul-2016)
  (1*R*,1′*R*,2*R*,2′*S*)-2,2′-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.
  $C_{65}H_{82}N_2O_{18}S_2$ 1243.48
  Other related compounds.