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Cisatracurium Besylate Injection

DEFINITION

Cisatracurium Besylate Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of cisatracurium ($C_{53}H_{72}N_2O_{12}$). Multiple-dose containers may contain benzyl alcohol.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197F**▲ (CN 1-May-2020)

Standard solution: 3 mg/mL of USP Cisatracurium Besylate RS in methylene chloride

Sample solution

[Note—If an emulsion forms during the extraction with methylene chloride, use a centrifuge to separate the layers.]

For Injections that do not contain benzyl alcohol: Nominally 2 mg/mL of cisatracurium from the Injection in methylene chloride prepared as follows. Transfer an amount of Injection equivalent to 10 mg of cisatracurium into a suitable separator, and extract with 5 mL of methylene chloride. Use the lower methylene chloride layer.

For Injections containing benzyl alcohol: Nominally 2 mg/mL of cisatracurium from the Injection in methylene chloride prepared as follows. Transfer an amount of Injection equivalent to 10 mg of cisatracurium into a suitable separator, and extract with 20.0 mL of ethyl acetate. Transfer the lower aqueous layer into another separator, and extract with 5 mL of methylene chloride. Use the lower methylene chloride layer.

Analysis

Samples: *Standard solution* and *Sample solution*

Add several drops of the *Standard solution* and *Sample solution* to separate potassium bromide plates. Allot the solvent to evaporate, and analyze the resulting residue.

Acceptance criteria: Meets the requirements

• **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**

Solution A: Acetonitrile, methanol, water, and anhydrous formic acid (21:21:60:1)

Mobile phase: 19.4 g/L of ammonium formate in *Solution A*. Filter under vacuum using a suitable filter.

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: Nominally 0.7 mg/mL of cisatracurium besylate from the Injection in *Diluent*, equivalent to 0.5 mg/mL of cisatracurium, prepared as follows. Using a “to contain” pipet, transfer a suitable volume of Injection to an appropriate volumetric flask, and dilute with *Diluent* to volume.

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: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—See *Table 1* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between *R-cis-R'-trans*-atracurium and cisatracurium, *System suitability solution*

Tailing factor: NMT 1.7 for cisatracurium, *Standard solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cisatracurium ($C_{53}H_{72}N_2O_{12}$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of cisatracurium from the *Sample solution*

r_S = peak response of cisatracurium from the *Standard solution*

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

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

M_{r1} = molecular weight of cisatracurium, 929.14

M_{r2} = molecular weight of cisatracurium besylate, 1243.48

Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

• **Benzyl Alcohol Content (if present)**

Internal standard solution: 4.5 mg/mL of decanol in ethyl acetate

Standard stock solution: 9.0 mg/mL of USP Benzyl Alcohol RS in water

Standard solution: 0.45 mg/mL of benzyl alcohol from the *Standard stock solution* prepared as follows. Transfer 5.0 mL of *Standard stock solution* and 20.0 mL of ethyl acetate into a 50-mL centrifuge tube. Stopper, shake well for 30 s, and allow the phases to separate. Transfer 10.0 mL of the top (organic) layer and 5.0 mL of the *Internal standard solution* into a 50-mL volumetric flask. Dilute with ethyl acetate to volume.

Sample solution: Transfer 5.0 mL of the Injection and 20.0 mL of ethyl acetate into a 50-mL centrifuge tube. Stopper, shake well for 30 s, and allow the phases to separate. Transfer 10.0 mL of the top (organic) layer and 5.0 mL of the *Internal standard solution* into a 50-mL volumetric flask. Dilute with ethyl acetate to volume.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 15-m fused-silica capillary column coated with a 1.0-µm layer of liquid phase G16

Temperatures

Detector: 250°

Injection port: 220°

Column: 140°

Carrier gas: Helium

Flow rate: 5.0 mL/min

Injection volume: 1 µL

Injection type: Split ratio, 2.5:1

System suitability

Sample: *Standard solution*

[Note—The relative retention times for decanol and benzyl alcohol are 0.62 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between decanol and benzyl alcohol

Relative standard deviation: NMT 2.0% for peak area ratios of benzyl alcohol to decanol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of benzyl alcohol in the portion of Injection taken:

$$\text{Result} = (R_U/R_S) \times (C_S/L) \times 100$$

R_U = peak area ratio of benzyl alcohol to the internal standard from the *Sample solution*

R_S = peak area ratio of benzyl alcohol to the internal standard from the *Standard solution*

C_S = concentration of USP Benzyl Alcohol RS in the *Standard stock solution* (mg/mL)

L = label claim of benzyl alcohol (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of benzyl alcohol

IMPURITIES

• **Organic Impurities**

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

Sensitivity solution: 0.4 µg/mL of USP Cisatracurium Besylate RS in *Diluent*

Analysis

Samples: *Standard solution, Sample solution,* and *Sensitivity solution*

Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response for each impurity from the *Sample solution*

r_S = peak response of cisatracurium from the *Standard solution*

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

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

M_{r1} = molecular weight of cisatracurium, 929.14

M_{r2} = molecular weight of cisatracurium besylate, 1243.48

Acceptance criteria: See *Table 1*. Disregard any peaks with responses less than the peak from the *Sensitivity solution*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Besylate[a]	0.10	—
cis-Quaternary acid[b]	0.13	4.3
(*R*)-*N*-Methyllaudanosine[c,d]	0.15	—
(*R*)-Laudanosine[e]	0.19	4.0
cis-Quaternary methyl ester[f,d] and benzyl alcohol[g]	0.22	—
cis-Quaternary alcohol[h]	0.27	5.0
Benzaldehyde[i]	0.40	—
R-trans-R'-trans-Atracurium[j,d]	0.72	—
R-cis-R'-trans-Atracurium[k,d]	0.88	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cisatracurium	1.0	—
trans-Monoquaternary compound[l,d]	1.19	—
trans-Monoacrylate[m,d]	1.30	—
cis-Monoquaternary compound[n,d]	1.42	—
cis-cis-Triester analog[o,d]	1.47	—
cis-Monoacrylate[p]	1.58	2.5
Any individual unspecified degradation product	—	0.2
Total degradation products	—	14.4

[a] This peak is due to the counterion and is not to be reported or included in *Total degradation products*.

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

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

[d] This is a process impurity that is included in the table for identification only. This impurity is controlled in the drug substance. It is not to be reported for the drug product and is not to be included in the total degradation products.

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

[f] (1*R*,2*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[2-(methoxycarbonyl)ethyl]-2-methyl-1-veratrylisoquinolinium benzenesulfonate.

[g] Benzyl alcohol co-elutes with *cis*-quaternary methyl ester. It is monitored using the test for *Benzyl Alcohol Content*.

[h] (1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(9-hydroxy-3-oxo-4-oxanonyl)-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate.

[i] Benzaldehyde is a degradant of benzyl alcohol and is not included in the total impurities.

[j] (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.

[k] (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.

[l] (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) dibenzenesulfonate.

[m] (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) benzenesulfonate.

[n] (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) dibenzenesulfonate.

[o] (1*R*,1'*R*,2*R*,2'*R*)-2,2'-(3,7,15-Trioxo-4,8,14-trioxa-heptadecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.

[p] (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) benzenesulfonate.

SPECIFIC TESTS

- **pH ⟨791⟩:** 3.0–3.8
- **Bacterial Endotoxins Test ⟨85⟩:** NMT 8.17 USP Endotoxin Units/mg of cisatracurium besylate
- **Sterility Tests ⟨71⟩:** Meets the requirements for the test for *Sterility of the Product to Be Examined, Membrane Filtration*
- **Other Requirements:** Meets the requirements for *Injections and Implanted Drug Products ⟨1⟩*

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass. Store in a cool place, protected from freezing and light.

• **USP Reference Standards** ⟨11⟩

USP Benzyl Alcohol RS

USP Cisatracurium Besylate RS

USP Cisatracurium Besylate System Suitability Mixture RS

Cisatracurium besylate.

R-trans-R'-trans-Atracurium:

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:

(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.

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

Topic/Question	Contact	Expert Committee
CISATRACURIUM BESYLATE INJECTION	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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