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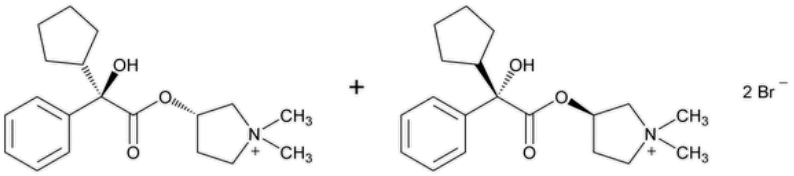
Glycopyrrolate

Change to read:



$C_{19}H_{28}BrNO_3$ ▲398.34▲ (USP 1-Dec-2019)

Pyrrolidinium, 3-[(*SR*)-(cyclopentylhydroxyphen ylacetyl)oxy]-1,1-dimethyl-, [*RS*-] bromide;

(*RS*)-[3-(*SR*)-Hydroxy-1,1-dimethylpyrrolidinium bromide] α-cyclopentylmandelate CAS RN®: ▲51186-83-5.▲ (USP 1-Dec-2019)

DEFINITION

Glycopyrrolate contains NLT 98.0% and NMT 102.0% of glycopyrrolate ($C_{19}H_{28}BrNO_3$), calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) ▲or ⟨197A⟩**:** Meets the requirements▲ (USP 1-Dec-2019)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Bromide***

  Sample solution: 25 mg/mL

  Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **Procedure**

  Buffer solution: Prepare a solution of 1.0 g of anhydrous sodium sulfate and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, and mix.

  Mobile phase: Acetonitrile, methanol, and *Buffer solution* (20:15:65)

  Standard solution: 0.1 mg/mL of USP Glycopyrrolate RS in *Mobile phase*

  Sample solution: 0.1 mg/mL of Glycopyrrolate in *Mobile phase*

  Chromatographic system

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

  Mode: LC

  Detector: UV 222 nm

  Column: 4.6-mm × 15-cm; 5-µm packing L1

  Column temperature: 40°

  Flow rate: 1.2 mL/min

  Injection volume: 50 µL

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  Tailing factor: NMT 2.0

  Relative standard deviation: ▲NMT 0.73%▲ (USP 1-Dec-2019)

  Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of glycopyrrolate ($C_{19}H_{28}BrNO_3$) in the portion of Glycopyrrolate taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.3%

Change to read:

• **Organic Impurities, Procedure 1**

[Note—On the basis of the synthetic route, perform either *Procedure 1* or *Procedure 2*. *Procedure 1* is recommended when ▲glycopyrrolate related compound A▲ (USP 1-Dec-2019) may be present (see *Table 2*); *Procedure 2* is recommended when didehydroglycopyrrolate, ▲glycopyrrolate related compound I,▲ (USP 1-Dec-2019) and ▲glycopyrrolate related compound L▲ (USP 1-Dec-2019) may be present (see *Table 4*).]

Buffer solution: Prepare a solution of 1.0 g of anhydrous sodium sulfate and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, and mix.

Diluent: Prepare a solution of 1.0 g of anhydrous sodium sulfate, 6.8 g of monobasic potassium phosphate, and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, 150 mL of methanol, and 200 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.8.

Solution A: Acetonitrile, methanol, and *Buffer solution* (20:15:65)

Solution B: Acetonitrile, methanol, and *Buffer solution* (50:15:35)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	100	0
25	10	90
35	10	90
37	100	0
45	100	0

Standard solution: 1.5 µg/mL each of USP Glycopyrrolate RS, USP Glycopyrrolate Related Compound A RS, USP Glycopyrrolate Related Compound B RS, and USP Glycopyrrolate Related Compound C RS in *Diluent*. Sonicate, if necessary, to facilitate dissolution.

Sample solution: 1.0 mg/mL of Glycopyrrolate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 222 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between glycopyrrolate and glycopyrrolate related compound B

Tailing factor: NMT 2.0 for the glycopyrrolate peak

Relative standard deviation: NMT 6.0% for each peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the glycopyrrolate related compounds A, B, and C in the portion of Glycopyrrolate taken:

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

r_U = peak response of each related compound from the *Sample solution*

r_S = peak response of the corresponding related compound from the *Standard solution*

C_S = concentration of the corresponding Reference Standard in the *Standard solution* (mg/mL)

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

Calculate the percentage of any other individual impurity in the portion of Glycopyrrolate taken:

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

r_U = peak response of each individual impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
▲Glycopyrrolate related compound A▲ (USP 1-Dec-2019)	0.45	0.15
Glycopyrrolate	1.00	—
▲Glycopyrrolate related compound B▲ (USP 1-Dec-2019)	1.14	0.15
▲Glycopyrrolate related compound C▲ (USP 1-Dec-2019)	2.68	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	0.50

▲ ▲ (USP 1-Dec-2019)

Change to read:

- **Organic Impurities, Procedure 2**

Buffer solution: 3.4 g/L of monobasic potassium phosphate in water (25 mM monobasic potassium phosphate buffer). Adjust with phosphoric acid to a pH of 2.5 ± 0.2.

Diluent: Acetonitrile and *Buffer solution* (1:1)

Solution A: *Buffer solution*

Solution B: Methanol

Mobile phase: See *Table 3*. Return to original conditions, and equilibrate the system.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
7	39	61
8	39	61
11	15	85
11.5	15	85

System suitability solution: 0.5 mg/mL of USP Glycopyrrolate RS and 1.0 µg/mL each of benzoic acid, USP Glycopyrrolate Related Compound B RS, USP Glycopyrrolate Related Compound C RS, USP Glycopyrrolate Related Compound I RS, and USP Glycopyrrolate Related Compound L RS in *Diluent*

Standard solution: 1.0 µg/mL of USP Glycopyrrolate RS in *Diluent*

Sample solution: 0.5 mg/mL of Glycopyrrolate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 45°

Flow rate: 0.42 mL/min

Injection volume: 2.5 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between glycopyrrolate and glycopyrrolate related compound B

Tailing factor: NMT 2.0 for the glycopyrrolate peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Glycopyrrolate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzoic acid	0.82	3.1	0.15
Didehydroglycopyrrolate[a]	0.89	1.0	0.15
Glycopyrrolate	1.00	—	—
▲Glycopyrrolate related compound B▲ (USP 1-Dec-2019)	1.06	1.4	0.15
▲Glycopyrrolate related compound I▲ (USP 1-Dec-2019)	1.22	1.4	0.15
▲Glycopyrrolate related compound C▲ (USP 1-Dec-2019)	1.32	1.9	0.15
▲Glycopyrrolate related compound L▲ (USP 1-Dec-2019)	1.52	1.8	0.15
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

▲ ▲ (USP 1-Dec-2019)

[a] 3-[2-(Cyclopent-1-en-1-yl)-2-hydroxy-2-phenylacetoxy]-1,1-dimethylpyrrolidin-1-ium bromide.

Change to read:

• **Limit of Erythro Isomer**

Buffer solution: 2.8 g/L of monobasic sodium phosphate in water. Adjust with ▲2.5 M sodium hydroxide▲ (USP 1-Dec-2019) to a pH of 6.50 ± 0.05.

Mobile phase: Methanol, acetonitrile, and *Buffer solution* (50:10:40)

System suitability solution: 40 µg/mL each of USP Glycopyrrolate Erythro Isomer RS and USP Glycopyrrolate RS in *Mobile phase*

Standard solution: 0.01 mg/mL of USP Glycopyrrolate RS in *Mobile phase*

Sample solution: 0.5 mg/mL of Glycopyrrolate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 222 nm

Column: 4.0-mm × 25-cm; 5-µm packing L45

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.2 between the ▲glycopyrrolate▲ (USP 1-Dec-2019) erythro isomer and glycopyrrolate, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 6.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲glycopyrrolate▲ (USP 1-Dec-2019) erythro isomer in the portion of Glycopyrrolate taken:

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

r_U = peak response of the ▲glycopyrrolate▲ (USP 1-Dec-2019) erythro isomer from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
▲Glycopyrrolate erythro isomer▲ (USP 1-Dec-2019)	0.89	0.4
Glycopyrrolate	1.00	—

▲ ▲ (USP 1-Dec-2019)

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at room temperature.

• **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Glycopyrrolate RS

USP Glycopyrrolate Erythro Isomer RS

(*RS*)-3-[(*RS*)-2-Cyclopentyl-2-hydroxy-2-phenylacetoxy]-1,1-dimethylpyrrolidinium bromide.

$C_{19}H_{28}BrNO_3$ 398.33

USP Glycopyrrolate Related Compound A RS

5-Nitrobenzene-1,3-dicarboxylic acid.

$C_8H_5NO_6$ 211.13

USP Glycopyrrolate Related Compound B RS

▲[Note—May be available as a free base or a hydrochloride salt.]▲ (USP 1-Dec-2019)

1-Methylpyrrolidin-3-yl-2-cyclopentyl-2-hydroxy-2-phenylacetate.

$C_{18}H_{25}NO_3$ 303.40

▲1-Methylpyrrolidin-3-yl-2-cyclopentyl-2-hydroxy-2-phenylacetate hydrochloride.

$C_{18}H_{25}NO_3 \cdot HCl$ 339.86▲ (USP 1-Dec-2019)

USP Glycopyrrolate Related Compound C RS

2-Cyclopentyl-2-hydroxy-2-phenylacetic acid.

$C_{13}H_{16}O_3$ 220.26

USP Glycopyrrolate Related Compound I RS

(*RS*)-3-[(*SR*)-2-(4-Chlorophenyl)-2-cyclopentyl-2-hydroxyacetoxy]-1,1-dimethylpyrrolidin-1-ium bromide.

$C_{19}H_{27}BrClNO_3$ 432.78

USP Glycopyrrolate Related Compound L RS

Methyl 2-cyclopentyl-2-hydroxy-2-phenylacetate.

$C_{14}H_{18}O_3$ 234.29

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

Topic/Question	Contact	Expert Committee
GLYCOPYRROLATE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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