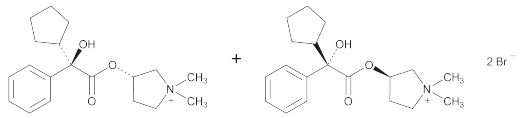
Glycopyrrolate

Change to read:



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

Pyrrolidinium, 3-[▲(*SR*)-▲*USP35*(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, ▲[*RS*-]▲*USP35* bromide; ▲(*RS*)-[3-(*SR*)-Hydroxy-1,1-dimethylpyrrolidinium bromide] α-cyclopentylmandelate▲*USP35* [596-51-0].

DEFINITION

Change to read:

Glycopyrrolate ▲▲*USP35* contains NLT 98.0% and NMT ▲ 102.0%▲*USP35* of glycopyrrolate ($C_{19}H_{28}BrNO_3$), ▲calculated on the dried basis.▲*USP35*

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩

Change to read:

• **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲*USP35*

• **C. Identification Tests—General,** *Bromide* ⟨191⟩
Sample solution: 25 mg/mL
Acceptance criteria: Meets the requirements

ASSAY

Change to read:

• **Procedure**
▲Buffer: 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* (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 1.0%
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▲*USP35*

IMPURITIES

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

Delete the following:

▲• **Ordinary Impurities** ⟨466⟩
Standard solutions: 0.05, 0.25, 0.5, and 1.0 mg/mL in alcohol
Sample solution: 50 mg/mL in alcohol
Eluant: A mixture of ethyl acetate, water, and anhydrous formic acid (74:16:10)
Adsorbent: Chromatographic silica gel
Application volume: 5 µL
Visualization: Dry the plate at 105° for 15 min, followed by Visualization Technique 3; then air-dry the developed plate at room temperature for 2 h.
Acceptance criteria: The intensity of any secondary spot of the *Sample solution* corresponds to NMT 0.5%, and the sum of the intensities of all secondary spots of the *Sample solution* corresponds to NMT 2.0%.▲*USP35*

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 5-nitroisophthalic acid (see *Table 2*) may be present; *Procedure 2* is recommended when didehydroglycopyrrolate, chloroglycopyrrolate, and methyl cyclopentylmandelate (see *Table 4*) may be present.]• (IRA 1-Jan-2013)
Buffer: 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

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of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.8.
Solution A: Acetonitrile, methanol, and *Buffer* (20:15:65)
Solution B: Acetonitrile, methanol, and *Buffer* (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 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 related compound 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 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 (%)
5-Nitroisophthalic acid[a]	0.45	0.15
Glycopyrrolate	1.00	—
Glycopyrrolate base[b]	1.14	0.15
Cyclopentylmandelic acid[c]	2.68	0.15
Any other individual impurity	—	0.10
Total impurities	—	0.50

[a] Glycopyrrolate related compound A.
[b] Glycopyrrolate related compound B.
[c] Glycopyrrolate related compound C.

▲*USP35*

Add the following:

•• **ORGANIC IMPURITIES: PROCEDURE 2**
Buffer: 3.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid (25 mM monobasic potassium phosphate buffer) to a pH of 2.5 ± 0.2.
Diluent: Acetonitrile and *Buffer* (1:1)
Solution A: *Buffer*
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

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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 base[b]	1.06	1.4	0.15
Chloroglycopyrrolate[c]	1.22	1.4	0.15
Cyclopentylmandelic acid[d]	1.32	1.9	0.15
Methyl cyclopentylmandelate[e]	1.52	1.8	0.15
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 3-[2-(Cyclopent-1-en-1-yl)-2-hydroxy-2-phenylacetoxy]-1,1-dimethylpyrrolidin-1-ium bromide.
[b] Glycopyrrolate related compound B.
[c] Glycopyrrolate related compound I.
[d] Glycopyrrolate related compound C.
[e] Glycopyrrolate related compound L.

● (IRA 1-Jan-2013)

Add the following:

▲• **LIMIT OF ERYTHRO ISOMER**

Buffer: 2.8 g/L of monobasic sodium phosphate in water. Adjust with a sodium hydroxide solution (1 in 10) to a pH of 6.50 ± 0.05.

Mobile phase: Methanol, acetonitrile, and *Buffer* (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: 10 µg/mL of USP Glycopyrrolate RS in *Mobile phase*

Sample solution: 500 µg/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 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 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 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 (%)
Erythro isomer (*R,R/S,S*-glycopyrrolate)[a]	0.89	0.4
Glycopyrrolate	1.00	—

[a] USP Glycopyrrolate Erythro Isomer RS.

▲*USP35*

SPECIFIC TESTS

Delete the following:

▲• **MELTING RANGE OR TEMPERATURE,** *Class I* ⟨**741**⟩**:** 193°–198°, but the range between beginning and end of melting does not exceed 2°.▲*USP35*

• **LOSS ON DRYING** ⟨**731**⟩

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers. ▲ Store at room temperature.▲*USP35*

Add the following:

•• **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.● (IRA 1-Jan-2013)

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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
1-Methylpyrrolidin-3-yl-2-cyclopentyl-2-hydroxy-2-phenylacetate.
$C_{18}H_{25}NO_3$ 303.40

USP Glycopyrrolate Related Compound C RS
2-Cyclopentyl-2-hydroxy-2-phenylacetic acid.
$C_{13}H_{16}O_3$ 220.26▲*USP35*

•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• (IRA 1-Jan-2013)

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