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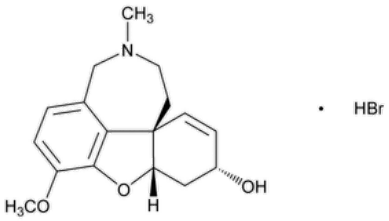
Galantamine Hydrobromide



$C_{17}H_{21}NO_3 \cdot HBr$ 368.27

6*H*-Benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4a*S*,6*R*,8a*S*)-; (4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide; (4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol hydrobromide CAS RN®: 1953-04-4.

DEFINITION

Galantamine Hydrobromide contains NLT 98.0% and NMT 102.0% of galantamine hydrobromide ($C_{17}H_{21}NO_3 \cdot HBr$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

[Note—Specimens are to be prepared using undried USP Galantamine Hydrobromide RS and the test article.]

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the *Assay*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Bromide***

Sample solution: 7 mg/mL of Galantamine Hydrobromide in water

Acceptance criteria: Meets the requirements of test *B*

ASSAY

- **Procedure**

Diluent: Methanol and water (5:95)

Buffer: 0.79 g/L of dibasic sodium phosphate dihydrate and 2.46 g/L of monobasic sodium phosphate anhydrous in water

Solution A: Methanol and *Buffer* (5:95)

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
6.0	100	0
20.0	95	5
35.0	85	15
50.0	80	20

Time (min)	Solution A (%)	Solution B (%)
51.0	40	60
55.0	40	60
56.0	100	0
60.0	100	0

System suitability solution: 1 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*

Standard solution: 1.0 mg/mL of USP Galantamine Hydrobromide RS in *Diluent*

Sample solution: 1.0 mg/mL of Galantamine Hydrobromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Column temperature: 55°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

[Note—For relative retention times, see *Table 2*.]

Suitability requirements

Resolution: NLT 4.5 between galantamine and 6*S*-galantamine, *System suitability solution*

Tailing factor: NMT 2.0 for galantamine, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of galantamine hydrobromide ($C_{17}H_{21}NO_3 \cdot HBr$) in the portion of Galantamine Hydrobromide 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 Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Delete the following:

▲• **Limit of Palladium:** Proceed as directed below or in *Elemental Impurities—Procedures ⟨233⟩*.

[Note—Perform this test only if palladium is a known inorganic impurity of the manufacturing process.]

Standard stock solution: 20 mg/L of palladium reference stock solution (NIST traceable) in water

Aqua regia: Under a hood, carefully mix hydrochloric acid and nitric acid (3:1).

[Note—To obtain each of the required Standard solutions, it is recommended that the required volume of *Standard stock solution* be mixed with a volume of *Aqua regia* equivalent to 5% of the final volume, followed by water.]

Standard solution A: 0.2 mg/L of palladium from the *Standard stock solution* in water

Standard solution B: 1.0 mg/L of palladium from the *Standard stock solution* in water

Standard solution C: 2.0 mg/L of palladium from the *Standard stock solution* in water

System suitability solution: Prepare a solution having a known concentration of 1.6 mg/L of palladium, as directed for the Standard solutions.

Sample solution: Weigh 1 g of Galantamine Hydrobromide. Transfer the sample to an appropriate digestion system, and digest using appropriate acids (e.g., nitric acid or mixtures of nitric acid and sulfuric acid and mixtures of nitric acid and hydrogen peroxide). After digestion, heat to dryness. Add 0.5 mL of *Aqua regia* and 2 mL of water. Warm gently to dissolve any residue. Allow to cool. Transfer quantitatively to a 10-mL volumetric flask, and dilute with water to volume.

Digestion blank solution: Prepare this solution following the procedure for the *Sample solution*, without the test article.

Instrumental conditions

(See *Atomic Absorption Spectroscopy ⟨852⟩*.)

Mode: Atomic absorption spectroscopy (flame)

Analytical wavelength: 247.6 nm (0.2-nm slit width)

Lamp: Palladium hollow-cathode

Blank solution: Dilute 5 mL of *Aqua regia* with water to 100 mL.

System suitability

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, *System suitability solution*, and *Blank solution*

Using the Standard solutions and *Blank solution*, construct a calibration curve.

Suitability requirements

Correlation coefficient: NLT 0.99

Recovery: 87.5%–112.5%, *System suitability solution*. [NOTE—Recovery is calculated using the calibration curve.]

Analysis

Samples: *Sample solution* and *Digestion blank solution*

Calculate the concentration of palladium in the *Sample solution*, using the calibration curve, corrected for the *Digestion blank solution* and the sample weight. Calculate the amount of palladium in the Galantamine Hydrobromide taken to prepare the *Sample solution*.

Acceptance criteria: NMT 10 ppm▲ (USP 1-May-2022)

• **ORGANIC IMPURITIES**

Diluent, Buffer, Solution A, Solution B, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.5 µg/mL of USP Galantamine Hydrobromide RS in *Diluent*

Standard solution: 5.0 µg/mL of USP Galantamine Hydrobromide RS in *Diluent*

Sample solution: 1000 µg/mL of Galantamine Hydrobromide in *Diluent*

System suitability

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

[NOTE—For relative retention times, see *Table 2*.]

Suitability requirements

Resolution: NLT 4.5 between galantamine and 6*S*-galantamine, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Galantamine Hydrobromide taken, on the dried basis:

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

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

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

C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (µg/mL)

C_U = concentration of the *Sample solution* (µg/mL)

F = relative response factor (see *Table 2*)

LOD = loss on drying (%)

Acceptance criteria: See *Table 2*. Disregard the bromide peak near the void volume. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
N-Desmethyl galantamine[a]	0.29	1.2	0.6
O-Desmethyl galantamine[b]	0.35	1.1	0.20
Galantamine *N*-oxide[c]	0.65	0.96	0.20
Dihydrogalantamine[d]	0.82	0.81	0.35
Galantamine	1.00	1.0	—
6*S*-Galantamine[e]	1.16	0.95	0.20
Narwedine[f]	1.64	1.9	0.15
Anhydrogalantamine[g]	2.05	1.2	0.40
Any unspecified impurity	—	1.0	0.10
Total impurities[h]	—	—	1.0

[a] (4a*S*,6*R*,8a*S*)-3-Methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.

[b] (4a*S*,6*R*,8a*S*)-11-Methyl-4a,5,9,10,11,12-Hexahydro-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-3,6-diol.

[c] (4a*S*,6*R*,8a*S*)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine 11-oxide.

[d] (4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,7,8,9,10,11,12-octahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.

[e] (4a*S*,6*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.

[f] (4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-one. This is a process impurity that may be found in Galantamine Hydrobromide isolated from a natural source.

[g] (4a*S*,8a*S*)-3-Methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine.

[h] Do not include the 4*R*,6*S*,8*R* isomer.

Change to read:

• **Limit of the 4*R*,6*S*,8*R* Isomer**

[Note—If Galantamine Hydrobromide is not isolated from a natural source, perform either *Procedure 1* or *Procedure 2*.]

Procedure 1

Background electrolyte solution: 8.9 g/L of dibasic sodium phosphate dihydrate in water. Adjust with phosphoric acid to a pH of 3.0.

Run buffer: 19.6 g/L of alpha-cyclodextrin hydrate in *Background electrolyte solution*. Pass the solution through a filter of 0.22-µm pore size.

Standard solution: 5 µg/mL of USP Galantamine Hydrobromide Racemic RS in water. Pass the solution through a filter of 0.22-µm pore size, discarding the first 8 mL.

Sample solution: 500 µg/mL of Galantamine Hydrobromide in water. Pass the solution through a filter of 0.22-µm pore size, discarding the first 8 mL.

Capillary rinse procedure: Use separate *Run buffer* vials for the capillary rinse and sample analysis. Proceed as directed in *Table 3*.

Table 3

Step #	Solution/Gas	Time (min)
1	0.1 N sodium hydroxide VS	15
2	Water	10

Step #	Solution/Gas	Time (min)
3	Suitable gas	5

[Note—If a new or dry capillary is being used, rinse with 1 N sodium hydroxide VS for 30 min, followed by rinsing with water for 15 min. Dry it with air or nitrogen for 10 min.]

Electrophoretic system

Mode: CE

Detector: UV 214 nm

Column: 75-µm × 60-cm uncoated fused silica

Column temperature: 20°

Applied voltage: 250 V/cm, positive polarity

Run time: 35 min

System suitability

Sample: *Standard solution*. [Note—For the purpose of identification, the *4S,6R,8S* isomer elutes at an approximate relative migration time (RMT) of 1.00, and the *4R,6S,8R* isomer elutes at an RMT of about 1.05.]

Measure the migration times and peak responses: the migration times for the *4R,6S,8R* isomer in the electropherograms of the *Sample solution* should not deviate by more than 5% of the migration time for the same component in the electropherogram of the *Standard solution*.

Suitability requirements

Resolution: NLT 2.5 between the two enantiomers

Relative standard deviation: NMT 10% for the *4R,6S,8R* isomer peak

Analysis

Samples: *Standard solution* and *Sample solution*

Injection: [Note—Rinse the capillary between injections as follows: water for 5 min, followed by *Run buffer* for 5 min. Rinse times are based on a rinse pressure of 1.4 bar.]

Sample solution: 34.5 mbar for 4 s

Run buffer: 6.9 mbar for 5 s

Calculate the corrected peak responses:

$$\text{Result} = (r/m)$$

r = peak response

m = migration time of the peak (min)

Calculate the limit of the *4R,6S,8R* isomer, in percent, in the portion of Galantamine Hydrobromide taken:

$$\text{Result} = (r_{CU}/r_{CS}) \times (C_S/C_U) \times P \times 100$$

r_{CU} = average corrected peak responses of the *4R,6S,8R* isomer from the *Sample solution*

r_{CS} = average corrected peak responses of the *4R,6S,8R* isomer from the *Standard solution*

C_S = concentration of USP Galantamine Hydrobromide Racemic RS in the *Standard solution* (µg/mL)

C_U = concentration of Galantamine Hydrobromide in the *Sample solution* (µg/mL)

P = chiral purity of USP Galantamine Hydrobromide Racemic RS, 0.5

Acceptance criteria: NMT 0.10% of the *4R,6S,8R* isomer

Procedure 2

[Note—Use low-actinic glassware and vials. It is recommended that precautions be taken to protect all solutions from light.]

Buffer: 8.2 g/L of anhydrous sodium acetate in water

Mobile phase: Acetonitrile and *Buffer* (2:98). Adjust with acetic acid to a pH of 6.5.

System suitability solution: 2.4 µg/mL of USP Galantamine Hydrobromide Racemic RS in water. [Note—This solution will contain about 1.2 µg/mL of the *4R,6S,8R* isomer.]

Sample solution: 1.2 mg/mL of Galantamine Hydrobromide in water

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.0-mm × 15-cm; 5-µm packing L41. [NOTE—Alternatively, a 2.0-mm × ▲15-cm▲ (USP 1-May-2022) column containing 5-µm packing L41 can be used with a recommended flow rate of about 0.2 mL/min.]

Flow rate: 0.8 mL/min

Injection volume: 5 µL

Run time: NLT 3 times the retention time of galantamine

System suitability

Sample: *System suitability solution*. [NOTE—The *4R,6S,8R* isomer elutes first as the minor peak followed by the major peak due to galantamine (which is the same as the *4S,6S,8S* isomer).]

Suitability requirements

Resolution: NLT 3.0 between the *4R,6S,8R* isomer and galantamine peaks

Relative standard deviation: NMT 5.0% for the *4R,6S,8R* isomer peak

Analysis

Sample: *Sample solution*

Calculate the percentage of *4R,6S,8R* isomer in the portion of Galantamine Hydrobromide taken:

$$\text{Result} = [r_{4R,6S,8R}/(r_{4R,6S,8R} + r_{4S,6R,8S})] \times 100$$

$r_{4R,6S,8R}$ = peak area of the *4R,6S,8R* isomer from the *Sample solution*

$r_{4S,6R,8S}$ = peak area of galantamine from the *Sample solution*

Acceptance criteria: NMT 0.10% of the *4R,6S,8R* isomer

SPECIFIC TESTS

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry at 105° for 4 h.

Acceptance criteria: NMT 0.5%

• **OPTICAL ROTATION ⟨781S⟩, *Procedures, Specific Rotation***

[NOTE—If Galantamine Hydrobromide is isolated from a natural source, perform the test for *Optical Rotation*.]

Sample solution: 20 mg/mL in water

Acceptance criteria: −90° to −100°

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Store at room temperature. Preserve in well-closed containers.

• **LABELING:** Label it to state if the source is naturally derived or is synthetic. If the source is not natural, perform either *Procedure 1* or *Procedure 2* of the test for the *Limit of the 4R,6S,8R Isomer.* If the source is natural, perform the test for *Optical Rotation ⟨781S⟩, Procedures, Specific Rotation*.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Galantamine Hydrobromide RS

USP Galantamine Hydrobromide Racemic RS

[NOTE—This is 50:50 mixture of the *4S,6R,8S* and *4R,6S,8R* isomers.]

(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol hydrobromide.
(4a*R*,6*S*,8a*R*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol hydrobromide.

$C_{17}H_{21}NO_3 \cdot HBr$ 368.27

USP Galantamine Hydrobromide Related Compounds Mixture RS

Contains a mixture of the following 5 compounds:

Galantamine hydrobromide.

Galantamine *N*-oxide;
(4a*S*,6*R*,8a*S*)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine 11-oxide.
$C_{17}H_{21}NO_4$ 303.35

Dihydrogalantamine;
(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,7,8,9,10,11,12-octahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.
$C_{17}H_{23}NO_3$ 289.37

6*S*-Galantamine;
(4a*S*,6*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.
$C_{17}H_{21}NO_3$ 287.35

Anhydrogalantamine;
(4a*S*,8a*S*)-3-Methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine.
$C_{17}H_{19}NO_2$ 269.34

[NOTE—The contents have previously been referred to as galantamine hydrobromide, 6β-hexahydrogalantamine, 6β-octahydrogalantamine, 6α-hexahydrogalantamine, and tetrahydrogalantamine, respectively.]

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

Topic/Question	Contact	Expert Committee
GALANTAMINE HYDROBROMIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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