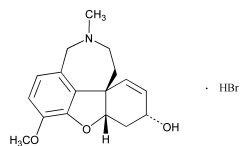


Add the following:

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*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide. [1953-04-4].

» Galantamine Hydrobromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{17}H_{21}NO_3 \cdot HBr$, calculated on the dried basis.

Packaging and storage—Store at room temperature. Preserve in well-closed containers.

USP Reference standards <11>—*USP Galantamine Hydrobromide RS*. *USP Galantamine Hydrobromide Related Compounds Mixture RS*. *USP Galantamine Hydrobromide Racemic RS*.

Identification—

A: *Infrared Absorption* (197K)—Specimens are to be prepared using undried USP Galantamine Hydrobromide RS and the test article.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Resolution solution*, as obtained in the *Assay*.

C: A solution of 7 mg per mL in water meets the requirement of the silver nitrate precipitate test for *Bromide* (191).

Loss on drying (731)—Dry at 105° for 4 hours; it loses not more than 0.5% of its weight.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method II (231): 0.002%.

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

Standard stock solution—Transfer an accurately measured quantity of palladium reference stock solution (NIST traceable), and dilute quantitatively with water to obtain a solution having a known concentration of about 20 mg per L.

Aqua regia—Carefully mix under a hood hydrochloric acid and nitric acid (3 : 1).

Standard solutions—Quantitatively dilute suitable volumes of *Standard stock solution* to obtain solutions having known concentrations of 0.2, 1.0, and 2.0 mg per L of palladium. [NOTE—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 to obtain each of the required *Standard solutions*.]

System suitability solution—Prepare a solution having a known concentration of 1.6 mg per L of palladium, as directed for *Standard solutions*.

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

Digestion blank solution—Prepare this solution following the procedure for *Test solution*, without the test article.

Test solution—Weigh accurately 1 g of Galantamine Hydrobromide. Transfer the sample into 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 upon rinsing with several mL of water into a 10-mL volumetric flask, and dilute with water to volume.

Atomic absorption spectrophotometer system—Use a standard atomic absorption spectrophotometric system (see *Spectrophotometry and Light Scattering* (851)) equipped with a palladium hollow-cathode lamp. Measure the absorbances in an air-acetylene flame at 247.6 nm (e.g., using a 0.2-nm slit width) of the *Blank solution* and the 0.2, 1.0, and 2.0 mg per L *Standard solutions*, and construct the calibration curve: the correlation coefficient must be not less than 0.99. Measure the absorbance of the *System suitability solution*, and calculate the concentration of the *System suitability solution*: the recovery is between 87.5% and 112.5% of the actual concentration.

Procedure—Measure the absorbance of the *Digestion blank solution* and the *Test solution*. Calculate the concentration of palladium in the *Test solution* using the calibration curve, after correcting appropriately for the absorbance of the *Digestion blank solution* and sample weight. Calculate the amount of palladium in the Galantamine Hydrobromide taken to prepare the *Test solution*: not more than 0.001% (w/w) of palladium is found.

Change to read:

Related compounds—

Buffer solution, Solution A, Solution B, Mobile phase, Resolution solution, Diluent, and Chromatographic system—Prepare as directed in the *Assay*.

Standard solution—Dilute the *Standard preparation* quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5.0 µg per mL of galantamine hydrobromide.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatograms. Identify the impurities, based on the relative retention times given in *Table 1*, and measure the peak responses. [NOTE—Ignore the peak due to bromide near the void volume and any peak below 0.05%. The approximate relative retention times in *Table 1* are for peak identification purposes only.] Calculate the percentage of each of the galantamine hydrobromide related compounds in the portion of Galantamine Hydrobromide, taken on the dried basis, by the formula:

$$100(C_S / C_U)(r_U / r_S)(1/F)(100/100 - L)$$

in which C_S and C_U are the concentrations, in mg per mL, of Galantamine Hydrobromide in the *Standard solution* and the *Test solution*, respectively; r_U is the peak response of each impurity obtained from the *Test solution*; r_S is the peak response of galantamine hydrobromide obtained from the *Standard solution*; F is the relative response factor for each of the impurities relative to galantamine hydrobromide; and L is the loss on drying, in percent, as determined in the test for *Loss on drying*. The limits are given in *Table 1*.

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (<i>F</i>)	Limit (% w/w)
¹ <i>N</i> -Desmethylgalantamine ¹	0.29	1.2	NMT 0.6 [•] (RB 15-Dec-2008)
² <i>O</i> -Desmethylgalantamine ²	0.35	1.1	NMT 0.20 [•] (RB 15-Dec-2008)
6β-Hexahydrogalantamine [•] (also known as Galantamine- <i>N</i> -oxide) ³ [•] (RB 15-Dec-2008)	0.65	0.96	[•] NMT 0.20 [•] (RB 15-Dec-2008)
6β-Octahydrogalantamine ^{•4} [•] (RB 15-Dec-2008)	0.82	0.81	NMT 0.35
Galantamine hydrobromide	1.00	1.0	—
6α-Hexahydrogalantamine [•] (also known as epigalantamine) ⁵ [•] (RB 15-Dec-2008)	1.16	0.95	[•] NMT 0.20 [•] (RB 15-Dec-2008)
Tetrahydrogalantamine ^{•6} [•] (RB 15-Dec-2008)	2.05	1.2	NMT 0.40
⁷ Narwedine ⁷	2.92	1.4	NMT 0.15 [•] (RB 15-Dec-2008)
Individual unspecified impurity	—	1.0	NMT 0.10
Total impurities ^{•8} [•] (RB 15-Dec-2008)	—	—	NMT 1.0

¹(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

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

³[4a*S*-(4a*α*,6β,8a*R*^{*})]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, *N*-oxide.

⁴[4a*S*-(4a*α*,6β,8a*R*^{*})]-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

⁵[4a*S*-(4a*α*,6α,8a*R*^{*})]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

⁶[4a*S*-(4a*R*^{*},8a*R*^{*})]-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-4a*H*-benzofuro[3a,3,2-*ef*][2]benzazepine.

⁷(4a*S*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-one.

⁸Do not include the 4*R*,8*R*-stereoisomer.[•] (RB 15-Dec-2008)

Assay—

Buffer solution—Dissolve 0.79 g of dibasic sodium phosphate dihydrate and 2.46 g of monobasic sodium phosphate anhydrous in 1 L of water.

Solution A—To 950 mL of the *Buffer solution*, pipet exactly 50 mL of methanol, and mix.

Solution B: acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

Diluent—Prepare a mixture of water and methanol (95 : 5).

Resolution solution—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 1 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide RS in *Diluent*, and dilute with *Diluent* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Galantamine Hydrobromide in *Diluent*, and dilute with *Diluent* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 10-cm column that contains 3.5-μm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 55°. The chromatograph is programmed as follows.

Time (minutes)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
0–6.0	100	0	isocratic

6.0–20.0	100→95	0→5	linear gradient
20.0–35.0	95→85	5→15	linear gradient
35.0–50.0	85→80	15→20	linear gradient
50.0–51.0	80→40	20→60	linear gradient
51.0–55.0	40	60	isocratic
55.0–56.0	40→100	60→0	linear gradient
56.0–60.0	100	0	re-equilibration

Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*. Identify the peaks using the relative retention times given in *Table 1*: the resolution, *R*, between galantamine and 6α-hexahydrogalantamine is not less than 4.5; the tailing factor for galantamine hydrobromide is not more than 2.0. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the responses for the galantamine hydrobromide peak. Calculate the quantity, in percent, of C₁₇H₂₁NO₃ · HBr in the portion of Galantamine Hydrobromide taken, by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which *C_S* and *C_U* are the concentrations of galantamine hydrobromide, in mg per mL, of the *Standard preparation* and the *Assay preparation*, respectively; and *r_U* and *r_S* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■₁₅ (USP31)