Galantamine Tablets

» Galantamine Tablets contain an amount of Galantamine Hydrobromide equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of galantamine ($C_{17}H_{21}NO_3$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

•**Labeling—**When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.• (RB 2-Nov-2009)

USP Reference standards ⟨11⟩**—***USP Galantamine Hydrobromide RS. USP Galantamine Hydrobromide Related Compounds Mixture RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—The spectrum of the *Test solution* corresponds to that of the *Standard solution,* as obtained in the test for *Uniformity of dosage units*.

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

Change to read:

Dissolution ⟨711⟩**—**

•TEST 1—•(RB 2-Nov-2009)

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Time: 20 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide RS in *Medium,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.008 mg per mL of galantamine for Tablets labeled to contain 4 mg; about 0.016 mg per mL of galantamine for Tablets labeled to contain 8 mg; and about 0.024 mg per mL of galantamine for Tablets labeled to contain 12 mg. [NOTE—The concentration of galantamine (free base), in mg per mL, can be calculated using the molecular weights of galantamine (287.35) and galantamine hydrobromide (368.27)]

Test solution—Use portions of the solution under test passed through a suitable 0.2-µm filter.

Procedure—Determine the amount of galantamine dissolved by employing UV absorption at the wavelength of maximum absorbance at about 288 nm on the *Test solution* in comparison with the *Standard solution,* using a 5-cm cell for Tablets labeled to contain 4 mg or 8 mg, or using a 1-cm cell for Tablets labeled to contain 12 mg. Calculate the percentage of galantamine ($C_{17}H_{21}NO_3$) dissolved, by the formula:

$$\frac{A_U \times C_S \times 500 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respecetively; C_S is the concentration of galantamine, in mg per mL, in the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—Not less than 80% (Q) of the labeled amount of galantamine is dissolved in 20 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium, Apparatus 2, Time, Standard solution, Test solution, and *Procedure*—Proceed as directed for *Test 1*.

Tolerances—Not less than 70% (Q) of the labeled amount of galantamine is dissolved in 20 minutes.• (RB 2-Nov-2009)

Uniformity of dosage units ⟨905⟩—meets the requirements for coated tablets.

Standard solution—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide RS in a suitable volumetric flask, and dilute quantitatively with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.04 mg of galantamine per mL. [NOTE—The concentration of galantamine (free base), in mg per mL, can be calculated using the molecular weights of galantamine (287.35) and galantamine hydrobromide (368.27).]

Test solution—Add one Tablet to each appropriately sized volumetric flask to obtain a final galantamine concentration of 0.04 mg per mL, add an appropriate amount of 0.1 N hydrochloric acid equivalent to 75% of the total volume of the volumetric flask, and mechanically shake for about 45 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a filter having a 0.2-µm or finer porosity, and use the filtrate.

Procedure—Determine the amount of galantamine ($C_{17}H_{21}NO_3$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 289 nm on filtered portions of the *Test solution* in comparison with the *Standard solution*. Calculate the quantity of galantamine ($C_{17}H_{21}NO_3$) dissolved, in percent of the label claim, by the formula:

$$(C_S / C_U)(A_U / A_S)100$$

in which C_S is the concentration, in mg per mL, of galantamine in the *Standard solution;* C_U is the concentration, in mg per mL, of galantamine in the *Test solution* based on the label claim; and A_U and A_S are the absorbances at the monitoring wavelength, obtained from the *Test solution* and the *Standard solution,* respectively.

Change to read:

Related compounds—

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

Resolution solution—Prepare a solution of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent* having a concentration of 0.6 mg per mL.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay*.

Test solution—Use the *Assay preparation.*

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph about 20 µL of the *Resolution solution,* and record the responses as directed for *Procedure*. Identify the impurities using the approximate relative retention times given in *Table 1:* the resolution, R, between 6β-hexahydrogalantamine and 6β-octahydrogalantamine is not less than 1.5. Chromatograph the *Standard solution,* and record the responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0% for the galantamine peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. [NOTE—Ignore the peak due to bromide near the void volume.] Calculate the percentage of each of the galantamine related compounds in the portion of Tablets taken by the formula:

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

in which C_S and C_U are the concentrations, in mg per mL, of galantamine in the *Standard solution* and *Test solution,* respectively; r_U is the peak area of each impurity obtained from the *Test solution;* r_S is the peak area of galantamine obtained from the *Standard solu-*

tion; and *F* is the relative response factor (see *Table 1* for values) for each of the impurities relative to galantamine.•

Table 1

Compound Name	Relative Retention Time (RRT)	Relative Response Factor (*F*)	Limit (%)
N-Desmethylgalantamine[1]	0.41	1.0	0.5
O-Desmethylgalantamine[2]	0.56	1.0	0.5
6β-Hexahydrogalantamime (also known as galantamine *N*-oxide)[3]	0.73	1.1	0.75
6β-Octahydrogalantamine (also known as lycoramine)†[4]	0.86	—	—
Galantamine hydrobromide	1.00	1.0	—
6α-Hexahydrogalantamine (also known as epigalantamine)[5]	1.15	1.0	0.5
Tetrahydrogalantamine†[6]	2.09	—	—
Individual unspecified degradation product	—	1.0	0.2
Total impurities	—	—	1.5

[NOTE—The impurities marked with "†" are not quantified and are intended for system suitability evaluation only.]
[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-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-3,6-diol.
[3][4a*S*-(4aα,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*-(4aα,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*-(4aα,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.

•[2]

Assay—

Buffer solution–Dissolve 5.34 g of dibasic sodium phosphate dihydrate in 1 L of water. Adjust with phosphoric acid to a pH of 6.5, and mix.

Solution A—Add 950 mL of *Buffer solution* to 50 mL of methanol, and mix.

Solution B—Prepare a mixture of acetonitrile and methanol (95 : 5).

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—Dissolve about 35.4 g of edetate disodium in 950 mL of water. Add 50 mL of methanol, and mix well.

Standard preparation—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.48 mg per mL of galantamine. [NOTE—The concentration of galantamine (free base), in mg per mL, can be calculated using the molecular weights of galantamine (287.35) and galantamine hydrobromide (368.27).]

Assay preparation—Weigh not fewer than 10 Tablets. Transfer an accurately weighed portion to an appropriately-sized volumetric flask, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a galantamine concentration of about 0.48 mg per mL, based on the label claim. Pass a portion of this solution through a PTFE filter having a 0.45-µm or finer porosity, and use the filtrate.

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-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0.0–40.0	100→75	0→25	linear gradient
40.0–45.0	75→60	25→40	linear gradient
45.0–46.0	60→40	40→60	linear gradient
46.0–55.0	40	60	isocratic
55.0–56.0	40→100	60→0	linear gradient
56.0–61.0	100	0	re-equilbration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

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 percentage of label claim, of galantamine ($C_{17}H_{21}NO_3$) in the portion of Tablets 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, in mg per mL, in 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.