Galantamine Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Substantive error, broad impact

In accordance with the Rules and Procedures of the Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Galantamine Tablets monograph. The purpose for the revision is to specify, in Dissolution Test 3, that the paddle position should be adjusted so that the distance between the tip of the peak (inside the peak vessel) and the bottom of the paddle is 1 cm rather than the default value of 2.5 cm specified within General Chapter <711> *Dissolution*.

The Galantamine Tablets Revision Bulletin supersedes the currently official monograph. The *Revision Bulletin* will be incorporated in the *Second Supplement* to *USP 39–NF 34*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301–998–6792 or hrj@usp.org).

Galantamine Tablets

DEFINITION

Galantamine Tablets contain an amount of Galantamine Hydrobromide equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of galantamine ($C_{17}H_{21}NO_3$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩:** The spectrum of the *Sample 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 of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**

Buffer solution: 5.34 g/L of dibasic sodium phosphate dihydrate in water. Adjust with phosphoric acid to a pH of 6.5.
Solution A: •Chromatographic methanol• (RB 1-Jan-2016) and *Buffer solution* (1:19)
Solution B: •Chromatographic acetonitrile• (RB 1-Jan-2016) and •chromatographic methanol• (RB 1-Jan-2016) (19:1)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40.0	75	25
45.0	60	40
46.0	40	60
55.0	40	60
56.0	100	0
61.0	100	0

Diluent: Dissolve 35.4 g of edetate disodium in 950 mL of water, and add 50 mL of •chromatographic methanol.• (RB 1-Jan-2016) [NOTE—First dissolve in water, and then add •chromatographic methanol.• (RB 1-Jan-2016)]
Standard solution: 0.62 mg/mL of USP Galantamine Hydrobromide RS in *Diluent*
Sample solution: 0.48 mg/mL of galantamine from powdered Tablets (NLT 10) in *Diluent*. Pass through a PTFE filter of 0.45-µm or finer pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 10-cm; 3-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 = nominal concentration of galantamine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

Test 1
Medium: Water; 500 mL
Apparatus 2: 50 rpm
Time: 20 min
Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in *Medium*, where *L* is the label claim in mg
Sample solution: Pass portions of the solution through a suitable filter of 0.2-µm pore size.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 288 nm
Cell: 5-cm cell for 4-mg and 8-mg Tablets; 1-cm cell for 12-mg Tablets
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Tolerances: NLT 80% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.
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, Sample solution, and **Analysis:** Proceed as directed for *Test 1*.
Tolerances: NLT 70% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
Medium: Water; 500 mL
Apparatus 2: 50 rpm. •Use peak vessels and adjust the position of the paddle so that the distance between the tip of the peak and the bottom of the paddle is 1 cm.• (RB 1-Jan-2016)
Time: 20 min
Buffer: Triethylamine and 3.45 g/L of monobasic sodium phosphate in water (1:1000). Adjust with phosphoric acid to a pH of 4.5.
Mobile phase: •Chromatographic acetonitrile, chromatographic methanol,• (RB 1-Jan-2016) and *Buffer* (10:10:80), filtered and deaerated
Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in water, where *L* is the label claim in mg
Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Use the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: Two times the retention time of galantamine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
•**Analysis**
Samples: *Standard solution* and *Sample solution*• (RB 1-Jan-2016)
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of the *Sample solution*
r_S = peak area of the *Standard solution*
C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Tolerances: NLT 80% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.

Change to read:

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩, •*Content Uniformity*• (RB 1-Jan-2016)
Standard solution: 0.05 mg/mL of USP Galantamine Hydrobromide RS in 0.1 N hydrochloric acid
Sample solution: Add 1 Tablet to each appropriately sized volumetric flask to obtain a final galantamine concentration of 0.04 mg/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 45 min. Dilute with 0.1 N hydrochloric acid to volume. Pass a portion of the solution through a suitable filter of 0.2-µm pore size, and use the filtrate.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: •Maximum absorbance• (RB 1-Jan-2016) at about 289 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in filtered portions of the *Sample solution* in comparison with the *Standard solution.*
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of the *Sample solution* (mg/mL)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Acceptance criteria: Meet the requirements for coated Tablets

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**
Buffer solution, Solution A, Solution B, Mobile phase, Diluent, Standard solution, and **Sample solution:** Prepare as directed in the *Assay*.
System suitability solution: 0.6 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Injection volume: 20 µL
System suitability
Samples: *Standard solution* and *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between 6*β*-hexahydrogalantamine and 6*β*-octahydrogalantamine, *System suitability solution*
Relative standard deviation: NMT 2.0% for galantamine, *Standard solution*
[NOTE—Identify the impurities using the approximate relative retention times given in *Table 2*.]
Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—Ignore the peak due to bromide near the void volume.]
Calculate the percentage of each of the impurities including the unspecified degradation impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (100/F)$$

r_U = peak area of each impurity from the *Sample solution*
r_S = peak area of galantamine from the *Standard solution*
C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of galantamine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27
F = relative response factor for each of the impurities relative to galantamine (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
N-Desmethylgalantamine[a]	0.41	1.1	0.5
6*β*-Hexahydrogalantamine (also known as galantamine *N*-oxide)[b]	0.73	1.1	0.75
6*β*-Octahydrogalantamine (also known as lycoramine)[c,d]	0.86	—	—
Galantamine hydrobromide	1.00	1.0	—
6*α*-Hexahydrogalantamine (also known as epigalantamine)[e]	1.15	1.1	0.5
Tetrahydrogalantamine[f,d]	2.09	—	—
Individual, unspecified degradation impurity	—	1.0	0.2
Total impurities	—	—	1.5

[a] (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.
[b] ● (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, *N*-oxide. ● (RB 1-Jan-2016)
[c] ● (4a*S*,6*R*,8a*S*)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol. ● (RB 1-Jan-2016)
[d] ● This is a process impurity and is listed for information only. It is controlled in the drug substance. ● (RB 1-Jan-2016)
[e] ● (4a*S*,6*S*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol. ● (RB 1-Jan-2016)
[f] ● (4a*S*,8a*S*)-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepine. ● (RB 1-Jan-2016)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Galantamine Hydrobromide RS
  USP Galantamine Hydrobromide Related Compounds Mixture RS
  Contains galantamine hydrobromide, 6*β*-hexahydrogalantamine, 6*β*-octahydrogalantamine, 6*α*-hexahydrogalantamine, and tetrahydrogalantamine.