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Galantamine Oral Solution

DEFINITION

Galantamine Oral Solution contains an amount of galantamine hydrobromide ($C_{17}H_{21}NO_3 \cdot HBr$) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of galantamine ($C_{17}H_{21}NO_3$). Galantamine Oral Solution also contains one or more suitable preservatives.

IDENTIFICATION

• **A.** 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**

▲▲ (USP 1-Aug-2020)

Solution A: Acetonitrile and water (1:99)

Solution B: 5 mg/mL of ammonium acetate in *Solution A*

Solution C: Acetonitrile

Solution D: Water

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)	Solution D (%)
0	50	3	47
25	50	35	15
27	50	3	47
32	50	3	47

Diluent: 5 mg/mL of ammonium acetate in water

System suitability solution: 0.26 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS prepared as follows. Transfer a suitable quantity of USP Galantamine Hydrobromide Related Compounds Mixture RS to a suitable flask, and dissolve in 3% of the flask volume of methanol. Dilute with *Diluent* to volume.

Standard solution: 0.26 mg/mL of USP Galantamine Hydrobromide RS (equivalent to 0.2 mg/mL of galantamine) prepared as follows. Transfer a suitable quantity of USP Galantamine Hydrobromide RS to an appropriate flask, and dissolve in 3% of the flask volume of methanol. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.2 mg/mL of galantamine from Oral Solution prepared as follows. Transfer a suitable volume of Oral Solution to an appropriate volumetric flask. Add 3% of the flask volume of methanol, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

▲▲ (USP 1-Aug-2020)

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 5 between galantamine and 6*S*-galantamine, ▲▲ (USP 1-Aug-2020) *System suitability solution*

Tailing factor: NMT 1.3, *Standard solution*

Relative standard deviation: NMT ▲1.0%,▲ (USP 1-Aug-2020) *Standard solution*

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 Oral Solution taken:

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

r_U = peak response ▲of galantamine▲ (USP 1-Aug-2020) from the *Sample solution*

r_S = peak response ▲of galantamine▲ (USP 1-Aug-2020) 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

• **DELIVERABLE VOLUME ⟨698⟩:** Meets the requirements

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

▲▲ (USP 1-Aug-2020)

Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.5 µg/mL of USP Galantamine Hydrobromide RS prepared as follows. Transfer a suitable quantity of USP Galantamine Hydrobromide RS to an appropriate flask, and dissolve in 3% of the flask volume of methanol. Dilute with *Diluent* to volume.

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 5 between galantamine and 6*S*-galantamine, ▲▲ (USP 1-Aug-2020) *System suitability solution*

Tailing factor: NMT 1.3, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Oral Solution taken:

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

r_U = peak response of each degradation product 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* (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: See *Table 2*. ▲The reporting threshold is 0.10%.▲ (USP 1-Aug-2020)

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
N-Desmethyl galantamine[a,b]	0.54	0.5
Galantamine *N*-oxide[c]	0.68	0.30
Dihydrogalantamine[d,e]	0.85	—
Galantamine	1.0	—
6*S*-Galantamine[f]	1.2	0.2
Narwedine[g,e]	1.6	—
▲Anhydrogalantamine▲ (USP 1-Aug-2020) [h,e]	2.0	—
Any unspecified degradation product	—	0.2
Total degradation products	—	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.▲ (USP 1-Aug-2020)

b This degradation product may be found if the drug substance is isolated from a natural source.

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.▲ (USP 1-Aug-2020)

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.▲ (USP 1-Aug-2020)

e This is a process impurity and is listed for information only. It is controlled in the drug substance. It is not to be reported and is not to be included in the total degradation products.

f ▲(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.▲ (USP 1-Aug-2020)

g ▲(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▲ (USP 1-Aug-2020) .

h ▲(4a*S*,8a*S*)-3-Methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine.▲ (USP 1-Aug-2020)

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^2 cfu/mL. The total yeasts and molds count does not exceed 5×10^1 cfu/mL. It meets the requirements of the test for absence of *Escherichia coli*.

• **pH ⟨791⟩:** 3.9–6.2

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature. Protect from freezing.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Galantamine Hydrobromide RS

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.]▲ (USP 1-AUG-2020)

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

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

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