Memantine Hydrochloride Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Memantine Hydrochloride Tablets monograph. The purpose for the revision is to widen the limit of memantine lactose adduct in the test for Limit of Memantine Lactose Adduct from NMT 0.7% to NMT 1.4% to accommodate a product approved by the FDA.

The Memantine Hydrochloride Tablets Revision Bulletin supersedes the previous Revision Bulletin, which became official on October 1, 2015. This Revision Bulletin will be incorporated in *USP 40–NF 35*.

Should you have any questions, please contact Mary P. Koleck, Ph.D., Scientific Liaison (301-230-7420 or mpk@usp.org).

Memantine Hydrochloride Tablets

DEFINITION

Memantine Hydrochloride Tablets contain an amount of memantine hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$).

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
  Analytical range: 4000–400 cm^{-1}
  Standard: 6.7 mg/mL of USP Memantine Hydrochloride RS in dichloromethane. Shake for 10 min, and pass through a suitable filter. Evaporate the solvent at room temperature. Collect the residue powder, and dry at 60° for 15 min. Prepare an approximate 1% (w/w) dispersion of the sample in potassium bromide.
  Sample: 6.7 mg/mL of memantine hydrochloride in dichloromethane. from NLT 20 crushed Tablets. Shake for 10 min, and centrifuge for 10 min. Pass the supernatant through a suitable filter. Evaporate the solvent at room temperature. Collect the residue powder, and dry at 60° for 15 min. Prepare an approximate 1% (w/w) dispersion of the sample in potassium bromide.
  Acceptance criteria: Fingerprint region of the *Standard* and *Sample* spectrum exhibit maxima at the same wave numbers.
- **B.** The retention time of the memantine peak of the *Sample solution* corresponds to that of the memantine peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
  Solution A: 200 mg/mL of sodium hydroxide in water
  Internal standard solution: 25 µg/mL of USP Amantadine Hydrochloride RS in water
  Standard stock solution: 25 µg/mL of USP Memantine Hydrochloride RS prepared as follows. Weigh a suitable quantity of the Standard into a volumetric flask. Add methanol to fill 40% of the final flask volume, and sonicate. Dilute with water to volume.
  Standard solution: Pipet 4.0 mL each of the *Internal standard solution* and the *Standard stock solution* into a test tube. Add 2 mL of *Solution A*, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 3 min. Allow the two layers to separate. Inject the toluene layer.
  Sample stock solution: Nominally 20 µg/mL of memantine hydrochloride prepared as follows. Transfer a suitable number of Tablets to a volumetric flask to obtain a 0.1 mg/mL memantine hydrochloride solution. Add methanol to fill 40% of the final flask volume, and sonicate for 30 min with intermittent shaking. Add water to fill 40% of the final flask volume, and sonicate for 30 min with intermittent shaking. Dilute with water to volume, and centrifuge a portion for 10 min. Pipet a suitable volume of the clear centrifugate into a volumetric flask, and dilute with water to volume.
  Sample solution: Pipet 5.0 mL of the *Sample stock solution*, 4.0 mL of the *Internal standard solution*, and 2 mL of *Solution A* into a test tube, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 5 min. Allow the two layers to separate. Inject the toluene layer.
  Blank: To 5.0 mL of 80 µL/mL of methanol in water add 2 mL of *Solution A*, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 5 min. Allow the two layers to separate. Inject the toluene layer.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: GC
  Detector: Flame ionization
  Column: 30-m × 0.32-mm; 0.25-µm packing G27
  Temperatures
  Injection port: 210°
  Detector: 300°
  Oven: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	20	140	0
140	30	200	5

  Carrier gas: Helium
  Flow rate: 34.8 psi
  Injection volume: 4 µL
  Injection type: Split ratio, 1:10
  System suitability
  Sample: *Standard solution*
  [NOTE—The relative retention times for amantadine and memantine are 0.97 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 2.0 between amantadine and memantine
  Tailing factor: NMT 2.5 for amantadine; NMT 2.0 for memantine
  Relative standard deviation: NMT 2.0% for the ratio of the peak areas of amantadine and memantine
  Analysis
  Samples: *Standard solution, Sample solution*, and *Blank*
  Calculate the percentage of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

  R_U = peak area ratio of memantine to amantadine from the *Sample solution*
  R_S = peak area ratio of memantine to amantadine from the *Standard solution*
  C_S = concentration of USP Memantine Hydrochloride RS in the *Standard solution* (µg/mL)
  C_U = nominal concentration of memantine hydrochloride in the *Sample solution* (µg/mL)
  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**
  Medium: 0.1 N hydrochloric acid with sodium chloride (2 g/L of sodium chloride in water), adjusted with hydrochloric acid to a pH of 1.2; 900 mL
  Apparatus 1: 100 rpm
  Time: 30 min
  Standard stock solution: (*L*/900) mg/mL of USP Memantine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet
  Internal standard solution: 28 µg/mL of USP Amantadine Hydrochloride RS in *Medium*

Standard solution
For Tablets labeled to contain 5 mg: Transfer 5 mL of the *Standard stock solution* to a test tube, add 1 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.
For Tablets labeled to contain 10 mg: Transfer 5 mL of the *Standard stock solution* to a test tube, add 2 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.
Sample solution: Pass a portion of the solution under test through a suitable filter.
For Tablets labeled to contain 5 mg: Transfer 5 mL of the filtrate to a test tube, add 1 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.
For Tablets labeled to contain 10 mg: Transfer 5 mL of the filtrate to a test tube, add 2 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: GC, splitless
Detector: Flame ionization
Column: 30-m × 0.32-mm; 0.25-µm packing G27
Flow rate: 34.8 psi
Temperatures
Injection port: 210°
Detector: 300°
Oven: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	20	140	0
140	30	200	5

Carrier gas: Helium
Injection volume: 4 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between amantadine and memantine
Tailing factor: NMT 2.0 each for amantadine and memantine
Relative standard deviation: •NMT 2.0% for the ratio of memantine to amantadine peaks• (RB 1-Oct-2015)
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) dissolved:

$$\text{Result} = (R_U/R_S) \times (C_S/L) \times V \times 100$$

R_U = peak area ratio of memantine to amantadine from the *Sample solution*
R_S = peak area ratio of memantine to amantadine from the *Standard solution*
C_S = concentration of USP Memantine Hydrochloride RS in the *Standard solution* (µg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
Tolerances: NLT 80% (*Q*) of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) is dissolved.

• **Uniformity of Dosage Units** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **Limit of Memantine–Lactose Adduct**
[Note—Perform this test if lactose is present in the formulation.]
Solution A: 40 mg/mL of sodium hydroxide in water
Buffer: Dissolve 3.3 g of monobasic potassium phosphate and 2.3 g of sodium 1-octane sulfonate in 1 L of water. Adjust with *Solution A* to a pH of 6.1.
Mobile phase: Acetonitrile, methanol, and *Buffer* (26:4:70)
Standard solution: 0.2 mg/mL of USP Memantine Hydrochloride RS in *Mobile phase*
Sample solution: Nominally 10 mg/mL of memantine hydrochloride from NLT 25 crushed Tablets, prepared as follows. Transfer an amount of powder equivalent to 100 mg of memantine hydrochloride to a 20-mL volumetric flask. Add 10 mL of *Mobile phase*, and sonicate for 30 min. Centrifuge, and pass a portion of the centrifugate through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Column: 40°
Detector: 35°
Flow rate: 1.3 mL/min
Injection volume: 50 µL
Run time: 1.3 times the retention time of the memantine peak
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 3.5
Relative standard deviation: NMT 10.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the memantine–lactose adduct in the portion of Tablets taken:

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

r_U = peak response of the memantine–lactose adduct from the *Sample solution*
r_S = peak response of memantine from the *Standard solution*
C_S = concentration of USP Memantine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of memantine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor of the memantine–lactose adduct (see *Table 3*)
Acceptance criteria: See *Table 3*.
Disregard all peaks other than the memantine–lactose adduct peak.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Memantine–lactose adduct	0.41	0.53	•1.4• (RB 1-Apr-2016)
Memantine	1.0	1.0	—

Change to read:

- **ORGANIC IMPURITIES**

Solution A: 1 N sodium hydroxide

System suitability stock solution A: 0.5 mg/mL each of USP Memantine Related Compound A RS, USP Memantine Related Compound B RS, USP Memantine Related Compound C RS, USP Memantine Related Compound D RS, and USP Memantine Related Compound E RS in *n*-hexane

System suitability stock solution B: Transfer 75 mg of USP Memantine Hydrochloride RS into a suitable container, add 9 mL of 1.0 N sodium hydroxide and 6 mL of *n*-hexane, and mix for 10 min.

System suitability solution: Pipet 4.0 mL of the *n*-hexane layer from *System suitability stock solution B* into a 10-mL volumetric flask. Add 0.5 mL of *System suitability stock solution A*, and dilute with *n*-hexane to volume.

Standard stock solution: 1.3 mg/mL of USP Memantine Hydrochloride RS in *n*-hexane prepared as follows. Weigh a suitable quantity of the Standard into a volumetric flask. Add *Solution A* to fill 30% of the final flask volume, and mix for 5 min. Add *n*-hexane to fill 40% of the final flask volume, and shake for 10 min. Transfer the contents of the flask into a separator. Allow the layers to separate, and filter a portion of the top *n*-hexane layer through anhydrous sodium sulfate. Use the clear solution.

Standard solution: Pipet 2.0 mL of the clear solution from the *Standard stock solution* into a 100-mL volumetric flask, and dilute with *n*-hexane to volume.

Sample solution: Nominally 5 mg/mL of memantine hydrochloride in *n*-hexane from NLT 20 crushed Tablets, prepared as follows. Transfer a weighed amount of powder equivalent to 100 mg of memantine hydrochloride to a suitable volumetric flask. Add *Solution A* to fill 15% of the final flask volume. Shake to disperse the material, and then shake for 5 min. Sonicate for 5 min with intermittent shaking. Add *n*-hexane to fill 20% of the final flask volume, and shake for 10 min. Transfer the contents into a separator. Allow the layers to separate, and filter a portion of the top hexane layer through anhydrous sodium sulfate. Use the clear solution.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 50-m × 0.32-mm; 0.52-µm packing G27
Temperatures
Injection port: 220°
Detector: 300°
Oven: See *Table 4*.

Table 4

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	5	145	0
145	10	250	20

Carrier gas: Helium
Flow rate: 4.0 ± 0.2 mL/min
Injection volume: 3 µL
Injection type: Split ratio, 1:20

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 5* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between memantine and memantine related compound B; NLT 2.0 between memantine related compound B and memantine related compound C, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of USP Memantine Related Compound E RS or any individual degradation product in the portion of Tablets taken:

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

r_U = peak response of USP Memantine Related Compound E RS or any individual degradation product from the *Sample solution*
r_S = peak response of memantine hydrochloride from the *Standard solution*
C_S = concentration of USP Memantine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of memantine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Memantine related compound A[a]	0.77	—
Memantine	1.0	—
Memantine related compound B[a]	1.03	—
Memantine related compound C[a]	1.1	—
Memantine related compound D[a]	1.2	—
Memantine related compound E	1.4	•0.3• (RB 1-Oct-2015)

[a] Process impurities controlled in the drug substance and are included for identification only. Not reported for the drug product and not included in the total impurities.
[b] Excludes memantine–lactose adduct monitored in the test for *Limit of Memantine–Lactose Adduct*.

Table 5 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	0.20
Total impurities[b]	—	0.5

[a] Process impurities controlled in the drug substance and are included for identification only. Not reported for the drug product and not included in the total impurities.

[b] Excludes memantine–lactose adduct monitored in the test for *Limit of Memantine–Lactose Adduct*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Amantadine Hydrochloride RS
  USP Memantine Hydrochloride RS
  USP Memantine Related Compound A RS
  1,3-Dimethyladamantane.
  $C_{12}H_{20}$ 164.29
  USP Memantine Related Compound B RS
  3,5-Dimethyladamantane-1-ol.
  $C_{12}H_{20}O$ 180.29
  USP Memantine Related Compound C RS
  1-Chloro-3,5-dimethyladamantane.
  $C_{12}H_{19}Cl$ 198.73
  USP Memantine Related Compound D RS
  1-Bromo-3,5-dimethyladamantane.
  $C_{12}H_{19}Br$ 243.18
  USP Memantine Related Compound E RS
  N-3,5-Dimethyladamantan-1-yl formamide.
  $C_{13}H_{21}NO$ 207.31