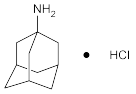
atomic weight of zirconium corrected for 2% hafnium content, 17.01 is the molecular weight of the hydroxide anion (OH), and 35.453 is the atomic weight of chlorine (Cl).

Amantadine Hydrochloride



$C_{10}H_{17}N \cdot HCl$ 187.71

Tricyclo[3.3.1.1^{3,7}]decan-1-amine, hydrochloride; 1-Adamantanamine hydrochloride [665-66-7].

DEFINITION

Amantadine Hydrochloride contains NLT 98.5% and NMT 101.5% of $C_{10}H_{17}N \cdot HCl$.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197S⟩
  Cell: 1 mm
  Sample solution: 50 mg in 10 mL of 0.1 N hydrochloric acid, and filter. Transfer the filtrate to a suitable separator, add 1 mL of 5 N sodium hydroxide, and extract with 5 mL of methylene chloride.
  Acceptance criteria: Meets the requirements

ASSAY

- **Procedure**
  Sample: Dissolve 120 mg of Amantadine Hydrochloride in a mixture of 30 mL of glacial acetic acid and 10 mL of mercuric acetate TS.
  Analysis: Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using suitable electrodes. Perform a blank determination. Each mL of 0.1 N perchloric acid is equivalent to 18.77 mg of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).
  Acceptance criteria: 98.5%–101.5%

IMPURITIES

- **Heavy Metals,** *Method I* ⟨231⟩
  Test preparation: Use 1 mL of 1 N acetic acid.
  Acceptance criteria: NMT 10 ppm
- **Organic Impurities**
  Internal standard solution: 50 mg/mL of adamantane in dichloromethane
  Standard solution: Transfer 10 mg of USP Amantadine Hydrochloride RS to a separator. Add 20 mL of 5.0 N sodium hydroxide and 18 mL of dichloromethane, and shake for 10 min. Remove the water layer, dry the organic layer by swirling with anhydrous sodium sulfate, and allow to stand for a few min to ensure that all remaining water has been removed. Filter, collect the filtrate in a 20-mL volumetric flask, add 0.2 mL of *Internal standard solution*, and dilute with dichloromethane to volume.
  Sample solution: Transfer 1.0 g of Amantadine Hydrochloride to a separator. Add 20 mL of 5.0 N sodium hydroxide and 18 mL of dichloromethane, and shake for 10 min. Remove the water layer, dry the organic layer by swirling with anhydrous sodium sulfate, and allow to stand for a few min to ensure that all remaining water has been removed. Filter, collect the filtrate in a 20-mL volumetric flask, add 0.2 mL of *Internal standard solution*, and dilute with dichloromethane to volume.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: GC
  Detector: Flame ionization
  Detector temperature: 300°
  Column: 0.53-mm × 30-m fused-silica column coated with 1.0-µm G27 stationary phase
  Column temperature: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	0	70	5
70	10	250	At least 17

  Carrier gas: Helium
  Flow rate: 4 mL/min
  Injection size: 2 µL
  Injector temperature: 220°
  Injection type:
  Split flow: 200 mL/min
  Split flow ratio: 50:1
  System suitability
  Sample: *Standard solution*
  [NOTE—The relative retention times for adamantane and amantadine are about 0.7 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 20 between adamantane and amantadine
  Relative standard deviation: NMT 5.0% determined from the peak response ratios of amantadine to adamantane
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of each impurity in the portion of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) taken:

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

  R_U = peak response ratio of each impurity to adamantane from the *Sample solution*
  R_S = peak response ratio of amantadine to adamantane from the *Standard solution*
  C_S = concentration of USP Amantadine Hydrochloride RS in the *Standard solution* (mg/mL)
  C_U = concentration of the *Sample solution* (mg/mL)
  Acceptance criteria
  Individual impurities: NMT 0.3%
  Total impurities: NMT 1.0%

SPECIFIC TESTS

- **pH** ⟨791⟩
  Sample: 0.2 g/mL in water
  Acceptance criteria: 3.0–5.5
- **Clarity and Color of Solution**
  Sample: Dissolve 2 g in 10 mL of water.
  Acceptance criteria: Solution is clear and nearly colorless.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards** ⟨11⟩
  USP Amantadine Hydrochloride RS

Amantadine Hydrochloride Capsules

DEFINITION

Amantadine Hydrochloride Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

IDENTIFICATION

- **Infrared Absorption** ⟨197S⟩
  Cell: 1 mm
  Sample solution: Place the contents of Capsules, equivalent to 200 mg of amantadine hydrochloride, in a vessel, dissolve in 0.1 N hydrochloric acid, and filter. Transfer the filtrate to

a separator, add 1 mL of 5 N sodium hydroxide, and extract with 5 mL of methylene chloride. Filter the extract through anhydrous sodium sulfate, and rinse the anhydrous sodium sulfate with 2 mL of methylene chloride.

ASSAY

- **PROCEDURE**

Internal standard solution: 0.4 mg/mL of naphthalene in hexane

Standard stock solution: 2 mg/mL of USP Amantadine Hydrochloride RS in water

Standard solution: Pipet 25.0 mL of *Standard stock solution* into a 250-mL separator, and add 25 mL of 2.0 N sodium hydroxide and 50.0 mL of *Internal standard solution*. Shake for 60 min, and collect the hexane layer (*Standard solution*).

Sample solution: Transfer NLT 20 Capsules to a 200-mL volumetric flask. Add 40 mL of 0.1 N hydrochloric acid, and heat gently to achieve complete dissolution. Cool, and dilute with water to volume. Pipet 5.0 mL of the solution into a 250-mL separator, and add 40 mL of 1.0 N sodium hydroxide and 50.0 mL of *Internal standard solution*. Shake for 60 min, and collect the hexane layer (*Sample solution*).

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 2-mm × 1.22-m; glass column packed with 10% phase G1 on 100- to 120-mesh support S1A

Temperature

Column: 115°

Injector: 250°

Detector block: 250°

Injection size: 1 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2 between napthalene and amantadine

Tailing factor: NMT 2.0 for the analyte peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{10}H_{17}N \cdot HCl$ in the portion taken:

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

R_U = peak response ratios from the *Sample solution*
R_S = peak response ratios from the *Standard solution*
C_S = concentration of USP Amantadine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨**711**⟩

Test 1: Procedure for a Pooled Sample

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Internal standard solution: 0.054 mg/mL of naphthalene in hexane

Standard stock solution: 0.1 mg/mL of USP Amantadine Hydrochloride RS in water

Standard solution: Pipet 15.0 mL of *Standard stock solution* into a 50-mL screw-capped test tube, add 5.0 mL of 5 N sodium hydroxide and 10.0 mL of *Internal standard solution*, and shake for 60 min. Collect the hexane layer.

Sample solution: Filter 15.0 mL of the solution under test, and place into a 50-mL screw-capped test tube. Pipet 5.0 mL of 5 N sodium hydroxide and 10.0 mL of the *Internal standard solution* into the test tube, and shake for 60 min. Collect the hexane layer (*Sample solution*).

Chromatographic system: Proceed as directed in the *Assay*.

Injection size: 2.5 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: NLT 75% (Q) of the labeled amount of $C_{10}H_{17}N \cdot HCl$ is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Water; 900 mL

Apparatus 2: 75 rpm, with sinkers. [NOTE—A suitable sinker is available as catalog number CAPWHT-2S from www.qla-llc.com or www.tabletdissolution.com or www.labhut.com.]

Time: 45 min

Internal standard solution: 0.06 mg/mL of naphthalene in hexanes

Standard stock solution: 0.12 mg/mL of USP Amantadine Hydrochloride RS in *Medium*

Standard solution: Transfer 60.0 mL of the *Standard stock solution* to a 200-mL volumetric flask. Add 20 mL of 5 N sodium hydroxide and 40.0 mL of *Internal standard solution*. Shake the flask for approximately 10 min, and allow the layers to separate. Use the top layer for injection. The final concentration is about 0.18 mg/mL.

Sample solution: Transfer 3.0 mL of the solution under test to a centrifuge tube. Add 1.0 mL of 5 N sodium hydroxide and 2.0 mL of *Internal standard solution*. Shake the tube for approximately 10 min, and allow the layers to separate. Use the top layer for injection.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-cm, 0.25-µm film, phase G1

Temperature

Oven: 100° for 3 min, to 200 ° at 10°/min, held at 200 ° for 2 min

Injector: 250°

Detector: 300°

Carrier gas: Helium, 1.4 mL/min

Flow rate: 20 mL/min

Injection size: 2 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2 between naphthalene and amantadine hydrochloride

Tailing factor: NMT 2.0 for amantadine hydrochloride

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amantadine hydrochloride released:

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

R_U = ratio of the peak areas from the *Sample solution*
R_S = average ratio of the peak areas from the *Standard solution*
C_S = concentration of amantadine hydrochloride in the *Standard stock solution* (mg/mL)
L = label claim (mg/capsule)
V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (Q) of the labeled amount of amantadine hydrochloride is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **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 Amantadine Hydrochloride RS

Amantadine Hydrochloride Oral Solution

» Amantadine Hydrochloride Oral Solution contains not less than 95.0 per cent and not more than 105.0 per cent of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Amantadine Hydrochloride RS

Identification, *Infrared Absorption* ⟨197S⟩**—**

Cell: 1 mm.

Solution—Place a volume of Oral Solution, equivalent to about 200 mg of amantadine hydrochloride, in a vessel, dissolve in 0.1 N hydrochloric acid, and filter. Transfer the filtrate to a separator, add 10 mL of 0.5 N sodium hydroxide, and extract with 5 mL of methylene chloride. Filter the extract through anhydrous sodium sulfate, and rinse the anhydrous sodium sulfate with 2 mL of methylene chloride.

Assay—

Internal standard solution, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Amantadine Hydrochloride Capsules*.

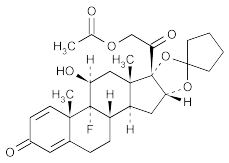
Assay preparation—Pipet 5.0 mL of the Oral Solution into a 250-mL conical flask, and add 45 mL of 1.0 N sodium hydroxide and 50.0 mL of *Internal standard solution*. Shake for 60 minutes, and collect the hexane layer (*Assay preparation*).

Procedure—Proceed as directed in the *Assay* under *Amantadine Hydrochloride Capsules*. Calculate the quantity, in mg, of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) in the portion of Oral Solution taken by the formula:

$$50C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Amantadine Hydrochloride RS in the *Standard preparation;* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Amcinonide



$C_{28}H_{35}FO_7$ 502.57

Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxy-, (11β,16α)-.

9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclopentanone, 21-acetate [51022-69-6].

» Amcinonide contains not less than 97.0 per cent and not more than 102.0 per cent of $C_{28}H_{35}FO_7$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—**
USP Amcinonide RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 40 µg per mL.

Medium: methanol.

Absorptivities at 238 nm, calculated on the dried basis, do not differ by more than 3.0%.

Specific rotation ⟨781S⟩: between +89.4° and +94.0°.

Test solution: 10 mg per mL, in chloroform.

Loss on drying ⟨731⟩**—**Dry it at 105° for 4 hours: it loses not more than 1.0% of its weight.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—

Solution A—Prepare a filtered and degassed mixture of water and acetonitrile (13:7).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and water (7:3).

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

System suitability solution—Dissolve suitable quantities of butylparaben and USP Amcinonide RS in *Solution B* to obtain separate solutions containing 12.5 µg per mL and 20 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Amcinonide RS in *Solution B,* and dilute quantitatively, and stepwise if necessary, with *Solution B* to obtain a solution having a known concentration of about 0.02 mg per mL.

Assay preparation—Transfer about 20 mg of Amcinonide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Solution B* to volume, sonicate for 5 minutes, and mix. Transfer 5 mL of this solution to a 50-mL volumetric flask, dilute with *Solution B* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1, and is programmed to provide variable mixtures of *Solution A* and *Solution B.* The flow rate is about 2 mL per minute. Equilibrate the system with *Solution A.* From 2.5 minutes to 10 minutes after injection, linearly increase the amount of *Solution B* to 100%. Chromatograph the *System suitability solution*, and record the peak responses as directed under *Procedure:* the relative retention times are about 0.78 for butylparaben and 1.0 for amcinonide, and the resolution, *R,* between butylparaben and amcinonide is not less than 8.0. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation*. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{28}H_{35}FO_7$ in the portion of Amcinonide taken by the formula:

$$1000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Amcinonide RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.