C: 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*.

Completeness of solution ⟨641⟩**—**The contents of 1 container dissolve in 10 mL of water to yield a clear solution.

Constituted solution—At the time of use, it meets the requirements for *Constituted Solutions* under *Injections* ⟨1⟩.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.10 USP Endotoxin Unit per mg of pralidoxime chloride.

pH ⟨791⟩: between 3.5 and 4.5, in a solution (1 in 20).

Other requirements—It meets the requirements for *Loss on drying* and *Heavy metals* under *Pralidoxime Chloride*. It also meets the requirements for *Sterility Tests* ⟨71⟩, *Uniformity of Dosage Units* ⟨905⟩, and *Labeling* under *Injections* ⟨1⟩.

Assay—

Dilute phosphoric acid solution, Tetraethylammonium chloride solution, Mobile phase, Standard preparation, System suitability preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Pralidoxime Chloride*.

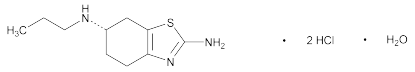
Assay preparation—Select an accurately counted number of containers of Pralidoxime Chloride for Injection, the combined contents of which are equivalent to about 10 g of pralidoxime chloride. Dissolve the contents of each container in water, and combine all of the solutions in a 1000-mL volumetric flask. Rinse each container with water, and add the rinsings to the volumetric flask. Dilute with water to volume, and mix. Transfer 25.0 mL of the resulting solution to a 200-mL volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Pralidoxime Chloride*. Calculate the quantity, in mg, of pralidoxime chloride ($C_7H_9ClN_2O$) in each container of Pralidoxime Chloride for Injection taken by the formula:

$$400(C / N)(r_U / r_S)$$

in which N is the number of containers selected for the *Assay preparation*, and the other terms are as defined therein.

Pramipexole Dihydrochloride



$C_{10}H_{17}N_3S \cdot 2HCl \cdot H_2O$ 302.26

Benzothiazole-2,6-diamine, 4,5,6,7-tetrahydro-*N*⁶-propyl-, dihydrochloride, monohydrate, (*S*)-;

(*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate [191217-81-9].

DEFINITION

Pramipexole Dihydrochloride contains NLT 98.0% and NMT 102.0% of $C_{10}H_{19}Cl_2N_3S$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨**197A**⟩ or ⟨**197M**⟩
  Wave number range: ⟨197A⟩, 3800 cm^{-1} to 650 cm^{-1}; ⟨197M⟩, 4000 cm^{-1} to 600 cm^{-1}
- **B.** The retention time of the major peak in the *Sample solution* corresponds to that of pramipexole (*S*-enantiomer) in the *System suitability solution* in the test for *Enantiomeric Purity*.
- **C. Identification Tests—General,** *Chloride* ⟨**191**⟩
  Sample: 1 mg/mL of Pramipexole Dihydrochloride in water
  Acceptance criteria: Meets the requirements of the silver nitrate precipitate test

ASSAY

- **Procedure**
  Solution A: Dissolve 9.1 g of potassium dihydrogen phosphate and 5.0 g of sodium 1-octanesulfonate monohydrate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.
  Solution B: Acetonitrile and *Solution A* (1:1)
  Diluent: Acetonitrile and *Solution A* (1:4)
  Mobile phase: See the gradient table below.

Time (min)	*Solution A* (%)	*Solution B* (%)
0	60	40
15	20	80
15.1	60	40
20	60	40

  System suitability solution: 1.5 mg/mL of USP Pramipexole Dihydrochloride RS and 0.8 mg/mL of USP Pramipexole Related Compound A RS in *Diluent*
  Standard solution: 1.5 mg/mL of USP Pramipexole Dihydrochloride RS in *Diluent*
  Sample solution: 1.5 mg/mL of Pramipexole Dihydrochloride in *Diluent*
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 264 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Column temperature: 40 ± 5°
  Flow rate: 1.5 mL/min
  Injection size: 5 µL
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times for pramipexole related compound A and pramipexole are about 0.7 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 6.0 between pramipexole related compound A and pramipexole, *System suitability solution*
  Tailing factor: NMT 2.0 for pramipexole, *System suitability solution*
  Relative standard deviation: NMT 1.0%, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of $C_{10}H_{19}Cl_2N_3S$ in the portion of Pramipexole Dihydrochloride 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 Pramipexole Dihydrochloride RS in the *Standard solution* (mg/mL)
  C_U = concentration of the *Sample solution* (mg/mL)
  M_{r1} = molecular weight of pramipexole dihydrochloride, 284.26
  M_{r2} = molecular weight of pramipexole dihydrochloride monohydrate, 302.26
  Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **Residue on Ignition** ⟨**281**⟩**:** NMT 0.10%
- **Heavy Metals,** *Method I* ⟨**231**⟩
  Standard solution: *Standard Lead Solution*, 10 ppm
  Sample solution: Ash 2 g of Pramipexole Dihydrochloride until an almost dry, carbonized mass is obtained. Cool the residue, add 2.0 mL of concentrated nitric acid and 5 drops of concentrated sulfuric acid, and carefully allow the fumes to evolve. Ignite at 500°–600° until the carbon is completely burned off. Cool the residue, add 4 mL of 6 M hydrochloric acid, cover the crucible, and digest on a

Official from May 1, 2012
Copyright (c) 2011 The United States Pharmacopeial Convention. All rights reserved.

boiling water bath for 15 min. Evaporate to dryness. Add one drop of concentrated hydrochloric acid and 10 mL of hot water, and digest for a further 2 min on the boiling water bath. Add 6 M ammonia solution dropwise until the solution is weakly alkaline, and adjust with 1 M acetic acid to a pH of 3.0–4.0. Filter the solution into a 25-mL volumetric flask, and dilute with water to 25 mL by washing the crucible and the filter.

Acceptance criteria: NMT 10 ppm

Organic Impurities

- **PROCEDURE**

Solution A, Solution B, Diluent, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 7.5 µg/mL of USP Pramipexole Dihydrochloride RS and 3 µg/mL of USP Pramipexole Related Compound A RS in *Diluent*

Standard solution: 1.5 µg/mL of USP Pramipexole Dihydrochloride RS in *Diluent*

Sample solution: 1.5 mg/mL of Pramipexole Dihydrochloride in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 6.0 between pramipexole related compound A and pramipexole, *System suitability solution*

Tailing factor: NMT 2.0 for pramipexole, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Pramipexole Dihydrochloride 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 impurity from the *Sample solution*

r_S = peak response of pramipexole from the *Standard solution*

C_S = concentration of USP Pramipexole Dihydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of pramipexole dihydrochloride monohydrate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of pramipexole dihydrochloride, 284.26

M_{r2} = molecular weight of pramipexole dihydrochloride monohydrate, 302.26

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Pramipexole propionamide[a]	0.5	0.15
Pramipexole related compound A[b]	0.7	0.15
Pramipexole	1.0	—
N-Propylpramipexole[c]	1.4	0.15
Pramipexole dimer[d]	1.7	0.15
Any other unidentified individual impurity	—	0.10

[a] (*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)propionamide.
[b] (*S*)-4,5,6,7-Tetrahydrobenzothiazole-2,6-diamine.
[c] (*S*)-2,6-Dipropylamino-4,5,6,7-tetrahydrobenzothiazole.
[d] N^6,$N^{6'}$-[2-Methylpentane-1,3-diyl]bis(4,5,6,7-tetrahydrobenzothiazole-2,6-diamine). This is a dimer of pramipexole (a mixture of four possible isomers).

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NLT 4.5% and NMT 6.5%
- **ENANTIOMERIC PURITY**

Mobile phase: *n*-Hexane, dehydrated alcohol, and diethylamine (850:150:1)

System suitability stock solution: 1 mg/mL each of USP Pramipexole Dihydrochloride RS and USP Pramipexole Related Compound D RS in dehydrated alcohol

System suitability solution: 0.01 mg/mL each of USP Pramipexole Dihydrochloride RS and USP Pramipexole Related Compound D RS from *System suitability stock solution* in *Mobile phase*

Standard stock solution: 2.0 mg/mL of USP Pramipexole Related Compound D RS in dehydrated alcohol

Standard solution: 1.5 µg/mL of USP Pramipexole Related Compound D RS in *Mobile phase*

Sample solution: 0.3 mg/mL, prepared by dissolving a suitable weighed quantity of Pramipexole Dihydrochloride in 25% of a flask volume of dehydrated alcohol and diluting with *Mobile phase* to volume

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 10-µm packing L51

Flow rate: 1.5 mL/min

Sample size: 75 µL

System suitability

Samples: *System suitability solution* [NOTE—The relative retention times for pramipexole related compound D (*R*-enantiomer) and pramipexole (*S*-enantiomer) are 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 5.0 between pramipexole related compound D and pramipexole, *System suitability solution*

Tailing factor: NMT 2.4 for pramipexole, *System suitability solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of pramipexole related compound D in the portion of Pramipexole Dihydrochloride taken:

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

r_U = peak response of pramipexole related compound D from the *Sample solution*

r_S = peak response of pramipexole related compound D from the *Standard solution*

C_S = concentration of pramipexole related compound D in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: NMT 1.0% of pramipexole related compound D

- **LIMIT OF PALLADIUM**

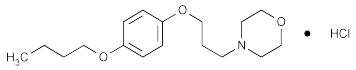
[NOTE—Perform this test if palladium is a known inorganic impurity.]

Official from May 1, 2012
Copyright (c) 2011 The United States Pharmacopeial Convention. All rights reserved.

Diluent: 0.1 M hydrochloric acid
Standard solution: 40 µg/L of palladium in *Diluent*, from commercially available palladium standard solution for atomic absorption/inductively coupled plasma. [NOTE—Freshly prepare this solution as required on the day of use.]
Sample solution: To 0.5 g of Pramipexole Dihydrochloride in a 50-mL volumetric flask add 5.00 mL of 1 M hydrochloric acid, and dissolve with heating. Cool to room temperature, and dilute with water to volume.
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩).
Mode: Atomic absorption spectrophotometry
Analytical wavelength: Palladium emission line at 247.6 nm
Lamp: Hollow cathode
Atomization source: Graphite furnace. [NOTE—Follow the manufacturer's recommended programming sequence.]
Sample size: 20 µL
Blank: *Diluent*
System suitability
Sample: *Standard solution*
Suitability requirements
Absorbance: NLT 0.034
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the concentration of palladium in the *Sample solution* by the standard addition method.
Acceptance criteria: NMT 5 ppm

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from moisture and light.
- **USP REFERENCE STANDARDS ⟨11⟩**
USP Pramipexole Dihydrochloride RS
USP Pramipexole Related Compound A RS
(*S*)-4,5,6,7-Tetrahydrobenzothiazole-2,6-diamine.
$C_7H_{11}N_3S$ 169.25
USP Pramipexole Related Compound D RS
(*R*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole.
$C_{10}H_{17}N_3S$ 211.33

Pramoxine Hydrochloride



$C_{17}H_{27}NO_3 \cdot HCl$ 329.86
Morpholine, 4-[3-(4-butoxyphenoxy)propyl]-, hydrochloride.
4-[3-(*p*-Butoxyphenoxy)propyl]morpholine hydrochloride [637-58-1].

» Pramoxine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{17}H_{27}NO_3 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—
USP Pramoxine Hydrochloride RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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*.

C: It meets the requirements of the tests for *Chloride* ⟨191⟩.

Melting range ⟨741⟩: between 170° and 174°.

Loss on drying ⟨731⟩—Dry it at 105° for 1 hour: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Assay—

pH 7.5 Phosphate buffer—Dissolve 8.71 g of dibasic potassium phosphate in about 800 mL of water, adjust with dilute phosphoric acid (1 in 10) to a pH of 7.5 ± 0.1, add water to make 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *pH 7.5 Phosphate buffer* (55:45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Pramoxine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Pramoxine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 40°, and the flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{27}NO_3 \cdot HCl$ in the portion of Pramoxine Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Pramoxine Hydrochloride 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.

Pramoxine Hydrochloride Cream

» Pramoxine Hydrochloride Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{27}NO_3 \cdot HCl$ in a suitable water-miscible base.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—
USP Pramoxine Hydrochloride RS

Identification—

A: Dissolve a quantity of Cream, equivalent to about 50 mg of pramoxine hydrochloride, in a mixture of 25 mL of methanol and 75 mL of ether, and extract with three 25-mL portions of a mixture of equal volumes of 3 N hydrochloric acid and water. Discard the methanol-ether solution, render the combined extracts alkaline with 25 mL of 5 N sodium hydroxide, and extract the pramoxine with 50 mL of chloroform. Evaporate the clear chloroform extract with the aid of a current of air to dryness: the UV absorption spectrum of a 1 in 100,000 solution of the residue so obtained, in 0.1 N hydrochloric acid, exhibits maxima and minima at the same wavelengths as that of a similar solution of the residue similarly obtained from USP Pramoxine Hydrochloride RS, concomitantly measured.

Official from May 1, 2012
Copyright (c) 2011 The United States Pharmacopeial Convention. All rights reserved.