Clonazepam, when dried, contains not less than 99.0\% of C₁₅H₂₉ClN₆O₄.

**Description** Clonazepam occurs as white to light yellow, crystals or crystalline powder.

It is sparingly soluble in acetic anhydride and in acetone, slightly soluble in methanol and in ethanol (95), very slightly soluble in diethyl ether, and practically insoluble in water.

It is gradually colored by light.

Melting point: about 240°C (with decomposition).

**Identification** (1) Determine the absorption spectrum of a solution of Clonazepam in methanol (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Clonazepam, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Perform the test with Clonazepam as directed under the Flame Coloration Test (2): a green color appears.

**Purity** (1) Chloride—To 1.0 g of Clonazepam add 50 mL of water, allow to stand for 1 hour with occasional shaking, and filter. Discard the first 20-mL portion of the filtrate, take the subsequent 20-mL portion of the filtrate, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution, and perform the test. Prepare the control solution as follows: to 0.25 mL of 0.01 mol/L hydrochloric acid VS add 6 mL of dilute nitric acid and water to make 50 mL (not more than 0.022%).

(2) Heavy metals—Proceed with 1.0 g of Clonazepam according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Dissolve 0.25 g of Clonazepam in 10 mL of acetone, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add acetone to make exactly 100 mL, then pipet 1 mL of this solution, add acetone to make exactly 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of nitromethane and acetone (10:1) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

**Loss on drying** Not more than 0.30\% (1 g, 105°C, 4 hours).

**Residue on ignition** Not more than 0.10\% (1 g).

**Assay** Weigh accurately about 0.5 g of Clonazepam, previously dried, dissolve in 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS = 31.572 mg of C₁₅H₂₉ClN₆O₄

**Containers and storage** Containers—Well-closed containers.

Storage—Light-resistant.

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**Clonidine Hydrochloride**

塩酸クロニジン

C₁₁H₁₇Cl₂N₄.HCl: 266.55
2-(2,6-Dichlorophenyl)iminomidazolidine monohydrochloride [4205-91-8]

Clonidine Hydrochloride, when dried, contains not less than 99.0\% of C₁₁H₁₇Cl₂N₄.HCl.

**Description** Clonidine Hydrochloride occurs as white crystals or crystalline powder.

It is freely soluble in methanol, soluble in water and in ethanol (95), slightly soluble in acetic acid (100), and practically insoluble in acetic anhydride and in diethyl ether.

**Identification** (1) To 5 mL of a solution of Clonidine Hydrochloride (1 in 1000) add 6 drops of Dragendorff's TS: an orange precipitate is formed.

(2) Determine the absorption spectrum of a solution of Clonidine Hydrochloride in 0.01 mol/L hydrochloric acid TS (3 in 10,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectrum of Clonidine Hydrochloride, previously dried, as directed in the potassium chloride disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(4) A solution of Clonidine Hydrochloride (1 in 50) responds to the Qualitative Tests for chloride.

**pH** Dissolve 1.0 g of Clonidine Hydrochloride in 20 mL of water: the pH of this solution is between 4.0 and 5.5.

**Purity** (1) Clarity and color of solution—Dissolve 1.0 g of Clonidine Hydrochloride in 20 mL of water: the solution is clear and colorless.

(2) Heavy metals—Proceed with 2.0 g of Clonidine Hydrochloride according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Arsenic—Prepare the test solution with 0.5 g of Clonidine Hydrochloride according to Method 3, and perform the test using Apparatus B (not more than 4 ppm).

(4) Related substances—Dissolve 0.20 g of Clonidine Hydrochloride in 2 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add methanol to make exactly 100 mL. Pipet 1 mL and 2
mL of this solution, to each add methanol to make exactly 20 mL, and use these solutions as the standard solution (1) and the standard solution (2), respectively. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 2 µL each of the sample solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, 1,4-dioxane, ethanol (99.5) and ammonia solution (28) (10:8:2:1) to a distance of about 12 cm, air-dry the plate, and then dry at 100°C for 1 hour. Spray evenly sodium hypochlorite TS on the plate, air-dry the plate for 15 minutes, and then spray evenly potassium iodide starch TS on the plate: the spots other than the principal spot and the spot of the starting point from the sample solution are not more intense than the spot from the standard solution (2), and the numbers of spots other than the principal spot and the spot of the starting point, which are more intense than the spot from the standard solution (1), are not more than 3.

**Loss on drying** Not more than 0.5% (1 g, 105°C, 4 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.4 g of Clonidine Hydrochloride, previously dried, and dissolve in 30 mL of acetic acid (100) by warming. After cooling, add 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS = 26.656 mg of C₁₇H₁₄Cl₂N₃HCl

**Containers and storage** Containers—Tight containers.

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**Cloperastine Hydrochloride**

塩酸クロベラスチン

C₂₀H₂₈ClNO.HCl: 366.32
1-[(RS)-(4-Chlorophenyl)phenylmethoxy]ethyl)piperidine monohydrochloride [14984-68-0]

Cloperastine Hydrochloride, when dried, contains not less than 98.5% of C₂₀H₂₈ClNO.HCl.

**Description** Cloperastine Hydrochloride occurs as white, crystals or crystalline powder.

It is very soluble in water, in methanol, in ethanol (95) and in acetic acid (100), and soluble in acetic anhydride.

A solution of Cloperastine Hydrochloride (1 in 10) shows no optical rotation.

**Identification** (1) Determine the absorption spectrum of a solution of Cloperastine Hydrochloride in 0.1 mol/L hydrochloric acid TS (1 in 2500) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum 1: both spectra exhibit similar intensities of absorption at the same wavelengths. Separate, determine the absorption spectrum of a solution of Cloperastine Hydrochloride in 0.1 mol/L hydrochloric acid TS (1 in 62,500) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum 2: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Cloperastine Hydrochloride, previously dried, as directed in the potassium chloride disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Shake 10 mL of a solution of Cloperastine Hydrochloride (1 in 100) with 2 mL of ammonia TS and 20 mL of diethyl ether, separate the water layer, wash the water layer with 20 mL of diethyl ether, and filter. Acidify the filtrate with dilute nitric acid: the solution responds to the Qualitative Test for chloride.

**Melting point** 148 – 152°C

**Purity** (1) Heavy metals—Proceed with 1.0 g of Cloperastine Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Related substances—Dissolve 0.040 g of Cloperastine Hydrochloride in 50 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 µL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area of both solutions by the automatic integration method: The areas of two peaks corresponding to the relative retention times about 0.8 and 3.0 to the retention time of cloperastine obtained from the sample solution are not larger than the peak area from the standard solution, respectively, and the area of the peak corresponding to the relative retention time about 2.0 to cloperastine is not larger than 5/3 of the peak area from the standard solution, and the areas of the peaks other than cloperastine and other than the peaks mentioned above are all not larger than 3/5 of the peak area from the standard solution. The total area of these peaks is not larger than 2 times of the peak area from the standard solution.

**Operating conditions**

- **Detector**: An ultraviolet absorption photometer (wavelength: 222 nm).
- **Column**: A stainless steel column about 5 mm in inside diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).
- **Column temperature**: A constant temperature of about 25°C.
- **Mobile phase**: A mixture of methanol, 0.1 mol/L monobasic potassium phosphate TS and perchloric acid (500:250:1).
- **Flow rate**: Adjust the flow rate so that the retention time of cloperastine is about 7 minutes.
- **Selection of column**: Dissolve 0.03 g of Cloperastine Hydrochloride and 0.04 g of benzophenone in 100 mL of