*N*-{2-[4-(2-Chloro-1,2-diphenylvinyl)phenoxy]ethyl}-*N*,*N*-diethylamine monocitrate [*50-41-9*]

Clomifene Citrate, when dried, contains not less than 98.0% of $C_{26}H_{28}ClNO.C_6H_8O_7$.

**Description** Clomifene Citrate occurs as a white to pale yellowish white powder. It is odorless.

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

It gradually changes in color by light.

Melting point: about 115°C

**Identification** (1) To 2 mL of a solution of Clomifene Citrate in methanol (1 in 200) add 2 mL of Reinecke salt TS: a light red precipitate is produced.

(2) Determine the absorption spectrum of a solution of Clomifene Citrate in 0.1 mol/L hydrochloric acid TS (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Clomifene Citrate Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) A solution of Clomifene Citrate in methanol (1 in 200) responds to the Qualitative Tests (1) and (2) for citrate salt.

**Purity** (1) Clarity and color of solution—A solution of 1.0 g of Clomifene Citrate in 30 mL of methanol is clear and colorless.

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

**Loss on drying** Not more than 1.0% (1 g, in vacuum, phosphorus (V) oxide, 3 hours).

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

**Isomer ratio** To 0.10 g of Clomifene Citrate add 10 mL of water and 1 mL of sodium hydroxide TS, and extract with three 15-mL portions of diethyl ether. Wash the combined diethyl ether extracts with 20 mL of water, add 10 g of anhydrous sodium sulfate to the combined diethyl ether extracts, shake for 1 minute, filter, and evaporate diethyl ether of the filtrate. Dissolve the residue in 10 mL of chloroform, and use this solution as the sample solution. Perform the test with 2 $\mu$L of the sample solution as directed under the Gas Chromatography according to the following conditions. Determine the areas of two adjacent peaks, $A_a$ and $A_b$, having retention times of about 20 minutes, where $A_a$ is the peak area of shorter retention time and $A_b$ is the peak area of longer retention time: $A_b/(A_a + A_b)$ is between 0.3 and 0.5.

*Operating conditions*—

Detector: A hydrogen flame-ionization detector.

Column: A column 3 mm in inside diameter and 1 m in length, having methylsilicone polymer coated at the ratio of 1% on siliceous earth for gas chromatography (125 to 150 $\mu$m in particle diameter).

Column temperature: A constant temperature of about 195°C.

Carrier gas: Nitrogen.

Flow rate: Adjust the flow rate so that the retention time of the peak for the first elution of clomifene citrate is about 20 minutes.

Selection of column: Proceed with 2 $\mu$L of the sample solution under the above operating conditions. Use a column giving the resolution between the two peaks being not less than 1.3.

**Assay** Weigh accurately about 1 g of Clomifene Citrate, previously dried, dissolve in 50 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of crystal violet TS). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 59.81 mg of $C_{26}H_{28}ClNO.C_6H_8O_7$

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

Storage—Light-resistant.

# Clomifene Citrate Tablets

クエン酸クロミフェン錠

Clomifene Citrate Tablets contain not less than 93% and not more than 107% of the labeled amount of the clomifene citrate ($C_{26}H_{28}ClNO.C_6H_8O_7$: 598.08).

**Method of preparation** Prepare as directed under Tablets, with Clomifene Citrate.

**Identification** (1) Weigh a portion of powdered Clomifene Citrate Tablets, equivalent to 1 g of Clomifene Citrate according to the labeled amount, shake vigorously with 100 mL of chloroform, and filter. Concentrate the filtrate on a water bath, allow to stand at room temperature, collect the crystals formed by filtration, and wash with a small quantity of chloroform. Proceed with the crystals as directed in the Identification (1) and (3) under Clomifene Citrate.

(2) Determine the absorption spectrum of a solution of the crystals obtained in (1) in 0.1 mol/L hydrochloric acid TS (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits maxima between 233 nm and 237 nm, and between 290 nm and 294 nm.

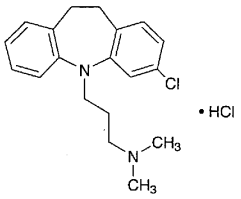
**Assay** Weigh accurately, and powder not less than 20 Clomifene Citrate Tablets. Weigh accurately a portion of the powder, equivalent to about 0.05 g of clomifene citrate ($C_{26}H_{28}ClNO.C_6H_8O_7$), add 50 mL of methanol, shake for 10 minutes, and add methanol to make exactly 100 mL. Centrifuge a portion of this solution, pipet 4 mL of the supernatant liquid, add methanol to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.05 g of Clomifene Citrate Reference Standard, previously dried in a desiccator (in vacuum, phosphorus (V) oxide) for 3 hours, and dissolve in methanol to make exactly 100 mL. Pipet 4 mL of this solution, and dilute with methanol to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, $A_T$ and $A_S$, of the sample solution and the standard solution, respectively, at 295 nm.

Amount (mg) of clomifene citrate ($C_{26}H_{28}ClNO.C_6H_8O_7$) = amount (mg) of Clomifene Citrate Reference Standard $\times \frac{A_T}{A_S}$

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

# Clomipramine Hydrochloride

塩酸クロミプラミン



$C_{19}H_{23}ClN_2.HCl$: 351.31
*N*-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl]-*N*,*N*-dimethylamine monohydrochloride
[*17321-77-6*]

Clomipramine Hydrochloride, when dried, contains not less than 98.5% of $C_{19}H_{23}ClN_2.HCl$.

**Description** Clomipramine Hydrochloride occurs as a white to pale yellow, crystalline powder. It is odor less.

It is very soluble in acetic acid (100), freely soluble in water, in methanol and in chloroform, soluble in ethanol (95), sparingly soluble in acetic anhydride, slightly soluble in acetone, and practically insoluble in ethyl acetate and in diethyl ether.

**Identification** (1) Dissolve 3 mg of Clomipramine Hydrochloride in 1 mL of nitric acid: a deep blue color develops.

(2) Determine the absorption spectrum of a solution of Clomipramine Hydrochloride in 0.1 mol/L hydrochloric acid TS (3 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.

(3) Take 1 g of Clomipramine Hydrochloride in a separator, dissolve in 10 mL of water, add 5 mL of sodium hydroxide TS, and extract with two 30-mL portions of diethyl ether [the water layer is used for Identification (4)]. Combine the diethyl ether extracts, add 20 mL of water, and shake. Take diethyl ether layer, dry with a small portion of anhydrous sodium sulfate, and filter. Evaporate the combined extracts by warming on a water bath, and proceed the test with the residue as directed under the Flame Coloration Test (2): a green color appears.

(4) The solution neutralized by adding dilute nitric acid to the water layer obtained in (3) responds to the Qualitative Tests for chloride.

**pH** Dissolve 1.0 g of Clomipramine Hydrochloride in 10 mL of water: the pH of this solution is between 3.5 and 5.0.

**Melting point** 192 - 196°C

**Purity** (1) Clarity and color of solution—Dissolve 1.0 g of Clomipramine Hydrochloride in 10 mL of water: the solution is clear and colorless to pale yellow.

(2) Heavy metals—Proceed with 2.0 g of Clomipramine Hydrochloride according to Method 2, 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 1.0 g of Clomipramine Hydrochloride according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.20 g of Clomipramine Hydrochloride in 10 mL of methanol, and use this solution as the sample solution. Separately, weigh 0.020 g of Imipramine Hydrochloride, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution (1). Then pipet 1 mL of the sample solution, and add methanol to make exactly 50 mL. Pipet 5 mL of the solution, add methanol to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 5 μL each of the sample solution, the standard solution (1) and the standard solution (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, acetone and ammonia solution (28) (15:5:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly potassium dichromate-sulfuric acid TS on the plate: the spot from the sample solution, corresponding to that from the standard solution (1), is not more intense than the spot from the standard solution (1). Each of the spots other than the principal spot and the above spot from the sample solution is not more intense than the spot from the standard solution (2).

**Loss on drying** Not more than 0.5% (1 g, 105°C, 3 hours).

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

**Assay** Weigh accurately about 0.5 g of Clomipramine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

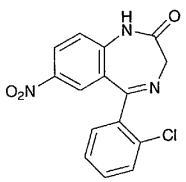
Each mL of 0.1 mol/L perchloric acid VS
= 35.132 mg of $C_{19}H_{23}ClN_2.HCl$

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

Storage—Light-resistant.

# Clonazepam

クロナゼパム



$C_{15}H_{10}ClN_3O_3$: 315.71
5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one [*1622-61-3*]