the solution of $n$-hexane prepared with 30 mL of water in the same manner as the blank: the absorbance is not more than 0.05.

**(8)** Readily carbonizable substances—Perform the test with 0.5 g of Citric Acid, provided that the solution is heated at 90°C for 1 hour: the solution has no more color than Matching Fluid K.

**Residue on ignition** Not more than 0.10% (2 g).

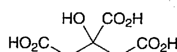
**Assay** Weigh accurately about 1.5 g of Citric Acid, dissolve in 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 70.05 mg of $C_6H_8O_7.H_2O$

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

# Anhydrous Citric Acid

無水クエン酸




$C_6H_8O_7$: 192.12
2-Hydroxypropane-1,2,3-tricarboxylic acid [*77-92-9*]

Anhydrous Citric Acid contains not less than 99.5% of $C_6H_8O_7$, calculated on the anhydrous basis.

**Description** Anhydrous Citric Acid occurs as colorless crystals, white granules or crystalline powder. It is odorless, and has a strong acid taste.

It is very soluble in water, freely soluble in methanol, in ethanol (95) and in acetone, and slightly soluble in diethyl ether.

**Identification** A solution of Anhydrous Citric Acid (1 in 20) changes the color of the blue litmus paper to red. The solution, made neutral with ammonia TS, responds to the Qualitative Tests for citrate.

**Purity (1)** Sulfate—Perform the test with 0.5 g of Anhydrous Citric Acid. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (not more than 0.048%).

**(2)** Oxalate—Dissolve 1.0 g of Anhydrous Citric Acid in 2 mL of dilute ethanol, neutralize with ammonia TS, add 0.2 mL of calcium chloride TS, and allow to stand for 1 hour: no turbidity is produced.

**(3)** Heavy metals—Proceed with 2.0 g of Anhydrous Citric Acid 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).

**(4)** Calcium—Dissolve 1.0 g of Anhydrous Citric Acid in 10 mL of water, neutralize with ammonia TS, and add 1 mL of ammonium oxalate TS: no turbidity is produced.

**(5)** Arsenic—Prepare the test solution with 2.0 g of Anhydrous Citric Acid according to Method 1, and perform the test using Apparatus B (not more than 1 ppm).

**(6)** Related substances—Dry 0.50 g of Anhydrous Citric Acid at 105°C for 3 hours. After cooling, dissolve the mass in exactly 10 mL of acetone, and use this solution as the sample solution. Perform the test with this solution as directed under the Paper Chromatography. Spot 5 $\mu$L of the sample solution on a filter paper. Develop the paper with the upper layer of a mixture of 1-butanol, formic acid and water (8:3:2) to a distance of about 25 cm, and air-dry the filter paper. Spray evenly bromophenol blue TS, pH 7.0, on the paper: any yellow spot other than the principal spot does not appear.

**(7)** Polycyclic aromatic hydrocarbon—Dissolve 25 g of Anhydrous Citric Acid in 30 mL of water by heating at about 50°C, cool, and extract with three 20-mL portions of hexane for ultraviolet-visible spectrophotometry. Each time separate the $n$-hexane layer by centrifuging between 2500 and 3000 revolutions per minute for 10 minutes. Combine the $n$-hexane extracts, and concentrate to 1 to 2 mL by evaporating. Cool, dilute with hexane for ultraviolet-visible spectrophotometry to make exactly 10 mL, and use this solution as the sample solution. Determine the absorbance between 260 nm and 350 nm as directed under the Ultraviolet-visible Spectrophotometry using the solution of $n$-hexane prepared with 30 mL of water in the same manner as the blank: the absorbance is not more than 0.05.

**(8)** Readily carbonizable substances—Perform the test with 0.5 g of Anhydrous Citric Acid, provided that the solution is heated at 90°C for 1 hour: the solution has no more color than Matching Fluid K.

**Water** Not more than 0.5% (2 g, direct titration).

**Residue on ignition** Not more than 0.10% (2 g).

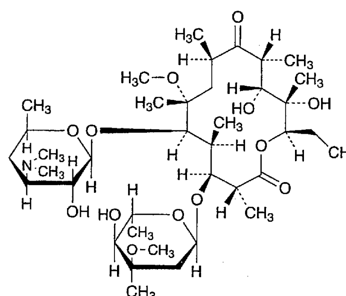
**Assay** Weigh accurately about 1.5 g of Anhydrous Citric Acid, dissolve in 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 64.04 mg of $C_6H_8O_7$

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

# Clarithromycin

クラリスロマイシン



$C_{38}H_{69}NO_{13}$: 747.95
(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-5-(3,4,6-Trideoxy-3-dimethylamino-$\beta$-D-*xylo*-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-$\alpha$-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxopentadecan-13-olide
[*81103-11-9*]

Clarithromycin contains not less than 900 μg (potency) per mg, calculated on the anhydrous basis. The potency of Clarithromycin is expressed as mass (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$).

**Description** Clarithromycin occurs as a white crystalline powder and has a bitter taste.

It is soluble in acetone and in chloroform, slightly soluble in methanol and in ethanol (95), and practically insoluble in water.

**Identification** **(1)** To 5 mg of Clarithromycin add 2 mL of sulfuric acid, and shake gently: a red-brown color develops.

**(2)** Dissolve 3 mg of Clarithromycin in 2 mL of acetone, and add 2 mL of hydrochloric acid: an orange color develops and changes immediately to red to deep purple.

**(3)** Determine the infrared absorption spectra of Clarithromycin and Clarithromycin Reference Standard as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wave numbers.

**(4)** Dissolve 0.01 g each of Clarithromycin and Clarithromycin Reference Standard in 4 mL of chloroform, and use these solutions as the sample solution and the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 5 μL each of the sample solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop with a mixture of chloroform, methanol and ammonia water (28) (100:5:1) to a distance of about 15 cm, and air-dry the plate. Spray evenly sulfuric acid on the plate, and heat at 105°C for 10 minutes: the principal spot from the sample solution and the spot from the standard solution show a dark purple color and have the same *Rf* value.

**Optical rotation** $[\alpha]_D^{20}$: −87 – −97° (0.25 g calculated on the anhydrous basis, chloroform, 25 mL, 100 mm).

**Melting point** Being specified separately.

**Purity** **(1)** Heavy metals—Proceed with 2.0 g of Clarithromycin according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

**(2)** Arsenic—Being specified separately.

**(3)** Related substances—Being specified separately.

**Water** Not more than 2.0% (0.5 g, volumetric titration, direct titration).

**Residue on ignition** Not more than 0.10% (2.0 g).

**Assay** Weigh accurately an amount of Clarithromycin and Clarithromycin Reference Standard, equivalent to about 0.1 g (potency), and dissolve in the mobile phase to make exactly 20 mL. Pipet 2 mL each of these solutions, add exactly 2 mL of the internal standard solution, add the mobile phase to make 20 mL, and use these solutions as the sample solution and the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, $Q_T$ and $Q_S$, of the peak area of clarithromycin to that of the internal standard.

Amount [μg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$)

$$= \text{amount [mg (potency)] of Clarithromycin Reference Standard} \times \frac{Q_T}{Q_S} \times 1000$$

*Internal standard solution*—A solution of butyl parahydroxybenzoate in the mobile phase (1 in 20,000).

*Operating conditions*—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50°C.

Mobile phase: A mixture of diluted 0.2 mol/L potassium dihydrogenphosphate TS (1 in 3) and acetonitrile (13:7).

Flow rate: Adjust the flow rate so that the retention time of clarithromycin is about 8 minutes.

*System suitability*—

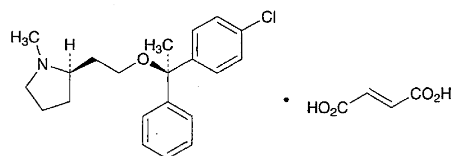
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, clarithromycin and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of clarithromycin to that of the internal standard is not more than 2.0%.

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

# Clemastine Fumarate

フマル酸クレマスチン




$C_{21}H_{26}ClNO.C_4H_4O_4$: 459.96

(2*R*)-2-{2-[(1*R*)-1-(4-Chlorophenyl)-1-phenylethoxy]ethyl}-1-methylpyrrolidine monofumarate [*14976-57-9*]

Clemastine Fumarate, when dried, contains not less than 98.5% of $C_{21}H_{26}ClNO.C_4H_4O_4$.

**Description** Clemastine Fumarate occurs as a white, crystalline powder. It is odorless.

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

**Identification** **(1)** To 5 mg of Clemastine Fumarate add 5 mL of sulfuric acid, and shake to dissolve: a yellow color develops. Slowly drop this solution into 10 mL of water: the yellow color immediately disappears.

**(2)** To 0.01 g of Clemastine Fumarate add 1 mL of fum-