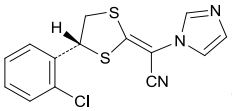
Lanoconazole

ラノコナゾール



and enantiomer

$C_{14}H_{10}ClN_3S_2$: 319.83

(2*E*)-2-[(4*RS*)-4-(2-Chlorophenyl)-1,3-dithiolan-2-ylidene]-2-(1*H*-imidazol-1-yl)acetonitrile

[*101530-10-3*]

Lanoconazole, when dried, contains not less than 98.0% and not more than 102.0% of lanoconazole ($C_{14}H_{10}ClN_3S_2$).

Description Lanoconazole occurs as white to pale yellow, crystals or crystalline powder.

It is soluble in acetone, sparingly soluble in methanol and in ethanol (99.5), and practically insoluble in water.

It is gradually colored to yellow by light.

A solution of Lanoconazole in acetone (1 in 25) shows no optical rotation.

Identification **(1)** To 0.1 g of Lanoconazole add 0.5 g of sodium hydroxide, heat gradually to melt, and carbonize. After cooling, add 10 mL of dilute hydrochloric acid: the gas evolved darkens moistened lead (II) acetate paper.

(2) Perform the test with Lanoconazole as directed under Flame Coloration Test <*1.04*> (2): a green color appears.

(3) Determine the absorption spectrum of a solution of Lanoconazole in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Lanoconazole RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared absorption spectrum of Lanoconazole, previously dried, as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of dried Lanoconazole RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point <*2.60*> 141 – 146℃

Purity **(1)** Heavy metals <*1.07*>—Proceed with 2.0 g of Lanoconazole 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) Related substances—Conduct this procedure using light-resistant vessels. Dissolve 0.10 g of Lanoconazole in 100 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method: the total area of the peaks other than lanoconazole obtained from the sample solution is not larger than 1/2 times the peak area of lanoconazole from the standard solution.

Operating conditions—

Detector, column, and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 0.576 g of sodium 1-nonanesulfonate in 1000 mL of a mixture of methanol, water and acetic acid (100) (55:44:1).

Flow rate: Adjust so that the retention time of lanoconazole is about 7 minutes.

Time span of measurement: About 3 times as long as the retention time of lanoconazole, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 2.5 mL of the standard solution, and add methanol to make exactly 50 mL. Confirm that the peak area of lanoconazole obtained with 5 μL of this solution is equivalent to 3.5 to 6.5% of that with 5 μL of the standard solution.

System performance: Put 20 mL of the sample solution in a colorless vessel, and expose to ultraviolet light (main wavelength: 365 nm) for 30 minutes. When the procedure is run with 5 μL of this solution under the above operating conditions, the resolution between the peak of lanoconazole and the peak, having the relative retention time of about 0.8 to lanoconazole, is not less than 1.5.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of lanoconazole is not more than 1.0%.

Loss on drying <*2.41*> Not more than 0.4% (1g, 105℃, 2 hours).

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 50 mg each of Lanoconazole and Lanoconazole RS, both previously dried, and dissolve each in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, add methanol to make 50 mL, and use these solu-

tions as the sample solution and the standard solution. Perform the test with 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lanoconazole to that of the internal standard.

$$\text{Amount (mg) of lanoconazole } (C_{14}H_{10}ClN_3S_2) = M_S \times Q_T / Q_S$$

M_S: Amount (mg) of Lanoconazole RS taken

Internal standard solution—A solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 1000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column 4.6 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℃.

Mobile phase: A mixture of methanol and water (11:9).

Flow rate: Adjust so that the retention time of lanoconazole is about 9 minutes.

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, lanoconazole 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 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of lanoconazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

Storage—Light-resistant.

Add the following to 9.01 Reference Standards (1):

Lanoconazole RS

Add the following to 9.41 Reagents, Test Solutions:

Diisopropyl 1,3-dithiolan-2-ylidenemalonate

$C_{12}H_{18}O_4S_2$ White crystals.

Identification—Determine the absorption spectrum of a solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate in methanol (1 in 125,000) as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 304 nm and 308 nm.

Melting point <2.60>: 54 – 57℃