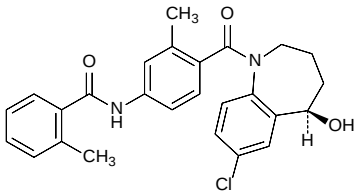
Tolvaptan

トルバプタン



and enantiomer

$C_{26}H_{25}ClN_2O_3$: 448.94

N-{4-[(5*RS*)-7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-carbonyl]-3-methylphenyl}-2-methylbenzamide [*150683-30-0*]

Tolvaptan contains not less than 98.5% and not more than 101.5% of tolvaptan ($C_{26}H_{25}ClN_2O_3$: 448.94), calculated on the dried basis.

Description Tolvaptan occurs as white, crystals or crystalline powder.

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

A solution of Tolvaptan in methanol (1 in 50) shows no optical rotation.

Identification (1) Determine the absorption spectrum of a solution of Tolvaptan 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 Tolvaptan RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Tolvaptan 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 Tolvaptan RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity Related substances—Dissolve 40 mg of Tolvaptan in methanol to make 100 mL, and use this solution as the sample solution. Perform the test with 5 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peaks other than tolvaptan is not more than 0.10%. Furthermore, the total amount of the peaks other than tolvaptan is not more than 0.20%.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase A: A mixture of water and phosphoric acid (1000:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography and phosphoric acid (1000:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 20	60 → 20	40 → 80
20 － 25	20	80

Flow rate: 1.0 mL per minute.

Time span of measurement: For 25 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: To 1 mL of the sample solution add methanol to make 100 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, add methanol to make exactly 20 mL. Confirm that the peak area of tolvaptan obtained with 5 μL of this solution is equivalent to 3.5 to 6.5% of that with 5 μL of the solution for system suitability test.

System performance: Dissolve 15 mg of isoamyl parahydroxybenzoate in 50 mL of methanol. To 2 mL of this solution and 2 mL of the sample solution add methanol to make 20 mL. When the procedure is run with 5 μL of this solution under the above operating conditions, tolvaptan and isoamyl parahydroxybenzoate are eluted in this order with the resolution being not less than 3.

System repeatability: When the test is repeated 6 times with 5 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of tolvaptan is not more than 2.0%.

Loss on drying <*2.41*> Not more than 1.0% (1 g, 105℃, 2 hours).

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

Assay Weigh accurately about 50 mg each of Tolvaptan and Tolvaptan RS, both previously dried, add exactly 5 mL each of the internal standard solution, add methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add methanol to make exactly 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 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 tolvaptan to that of the internal standard.

$$\text{Amount (mg) of tolvaptan } (C_{26}H_{25}ClN_2O_3) = M_S \times Q_T / Q_S$$

M_S: Amount (mg) of Tolvaptan RS taken

Internal standard solution—A solution of hexyl parahydroxybenzoate in methanol (3 in 500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 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 25℃.

Mobile phase: A mixture of acetonitrile for liquid chromatography, water and phosphoric acid (600:400:1).

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

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, tolvaptan and the internal standard are eluted in this order with the resolution being not less than 15.

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 ratio of the peak area of tolvaptan to that of the internal standard is not more than 1.0%.

Containers and storage Containers — Well-closed containers.

Add the following to 9.01 Reference Standards (1):

Tolvaptan RS