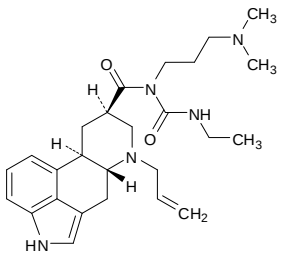
Cabergoline

カベルゴリン



$C_{26}H_{37}N_5O_2$: 451.60

(8*R*)-6-Allyl-*N*-[3-(dimethylamino)propyl]-*N*-(ethylcarbamoyl)ergoline-8-carboxamide

[*81409-90-7*]

Cabergoline contains not less than 98.0% and not more than 102.0% of cabergoline ($C_{26}H_{37}N_5O_2$), calculated on the anhydrous basis.

Description Cabergoline occurs as a white crystalline powder.

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

It is gradually colored to yellow by light.

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Cabergoline in ethanol (95) (1 in 30,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Cabergoline 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 Cabergoline 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 Cabergoline RS: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, dissolve Cabergoline and Cabergoline RS in ethanol (95), respectively, then evaporate the ethanol, dry the residues, and repeat the test on the residues.

Optical rotation *<2.49>* $[\alpha]_D^{20}$: −77 – −83° (0.1 g calculated on the anhydrous basis, ethanol (95), 50 mL, 100 mm).

Purity **(1)** Heavy metals *<1.07>*—Proceed with 1.0 g of Cabergoline 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).

(2) Related substances—Conduct this procedure using light-resistant vessels. Perform the test with 20 μL of the sample solution obtained in the Assay as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of them by the area percentage method: the amounts of related substances A and B, having the relative retention times of about 0.8 and about 2.8 to cabergoline are not more than 0.5%, respectively, and the amount of the peak other than cabergoline and the peaks mentioned above is not more than 0.1%. Furthermore, the total amount of the peaks other than cabergoline is not more than 1.5%.

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 4 times as long as the retention time of cabergoline, beginning after the solvent peak.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Use the diluted sample solution (1 in 500) as the solution for system suitability test. Pipet 5 mL of the solution for system suitability test, and add the mobile phase to make exactly 20 mL. Confirm that the peak area of cabergoline obtained with 20 μL of this solution is equivalent to 18 to 32% of that with 20 μL of the solution for system suitability test.

System repeatability: When the test is repeated 6 times with 20 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of cabergoline is not more than 2.0%.

Water *<2.48>* not more than 0.5% (1 g, volumetric titration, direct titration).

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 30 mg each of Cabergoline and Cabergoline RS (separately determine the water *<2.48>* in the same manner as Cabergoline), dissolve each in the mobile phase to make exactly 25 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, A_T and A_S, of cabergoline in each solution.

Amount (mg) of cabergoline ($C_{26}H_{37}N_5O_2$) = $M_S \times A_T / A_S$

M_S: Amount (mg) of Cabergoline RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

Mobile phase: Dissolve 6.8 g of potassium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To this solution add 0.2 mL of triethylamine. To 840 mL of this solution add 160 mL of acetonitrile.

Flow rate: Adjust so that the retention time of cabergoline is about 12 minutes.

System suitability—

System performance: Suspend 50 mg of Cabergoline in 10 mL of 0.1 mol/L sodium hydroxide TS, and stir for 15 minutes. To 1 mL of this solution add 1 mL of 0.1 mol/L hydrochloric acid TS, and add the mobile phase to make 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the peaks of related substance A having the relative retention time of about 0.8 to cabergoline and cabergoline is not less than 3.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of cabergoline is not more than 1.0%.

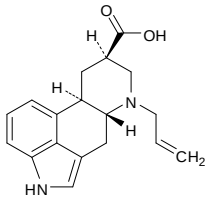
Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

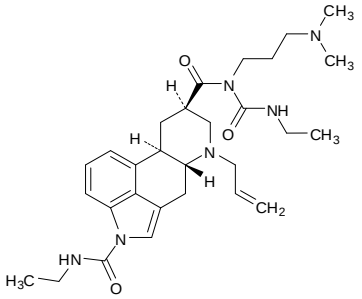
Related substance A:

(8*R*)-6-Allylergoline-8-carboxylic acid



Related substance B:

(8*R*)-6-Allyl-*N*-[3-(dimethylamino)propyl]-*N*,1-bis(ethylcarbamoyl)ergoline-8-carboxamide



Add the following to 9.01 Reference Standards (1):

Cabergoline RS