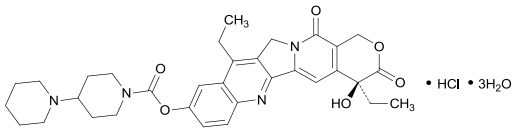
Irinotecan Hydrochloride Hydrate

イリノテカン塩酸塩水和物



$C_{33}H_{38}N_4O_6.HCl.3H_2O$: 677.18

(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl [1,4'-bipiperidine]-1'-carboxylate monohydrochloride trihydrate

[*136572-09-3*]

Irinotecan Hydrochloride Hydrate contains not less than 99.0% and not more than 102.0% of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6.HCl$: 623.14).

Description Irinotecan Hydrochloride Hydrate occurs as pale yellow to light yellow, crystals or crystalline powder.

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

It is gradually colored to yellow-brown and decomposed by light.

Melting point: about 255℃ (with decomposition).

Irinotecan Hydrochloride Hydrate shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Irinotecan Hydrochloride Hydrate in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Irinotecan Hydrochloride Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) To 1 g of Irinotecan Hydrochloride Hydrate add 50 mL of water, dissolve by warming, and cool: the solution responds to Qualitative Tests *<1.09>* (2) for chloride.

Optical rotation *<2.49>* $[\alpha]_D^{20}$: + 64 – + 69° (0.5 g calculated on the anhydrous basis, water, heat, after cooling, 50 mL, 100 mm).

pH *<2.54>* Dissolve 1 g of Irinotecan Hydrochloride Hydrate in 50 mL of water by warming, and cool: the pH of this solution is between 3.5 and 4.5.

Purity **(1)** Heavy metals *<1.07>*—Proceed with 2.0 g of Irinotecan Hydrochloride Hydrate 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).

(2) Related substances—Dissolve 50 mg of Irinotecan Hydrochloride Hydrate in a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) and 1 mL of 1 mol/L hydrochloric acid TS to make 20 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make exactly 100 mL, and use this solution as the standard solution. 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. Determine each peak area by the automatic integration method: the peak areas of related substances A and B, having the relative retention time of about 0.8 to irinotecan, and related substances C and D, having the relative retention time of about 1.6, obtained from the sample solution are not larger than 1/5 times the peak area of irinotecan from the standard solution, and the area of the peak other than irinotecan and the peaks mentioned above from the sample solution is not larger than 1/10 times the peak area of irinotecan from the standard solution. Furthermore, the total area of the peaks other than irinotecan from the sample solution is not larger than 4/5 times the peak area of irinotecan from the standard solution.

Operating conditions—

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

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase: Dissolve 1.22 g of sodium 1-decanesulfonate in a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and acetonitrile (6:4:3) to make 1000 mL.

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

Time span of measurement: About 3 times as long as the retention time of irinotecan.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of diluted 0.1 mol/L potassium dihydrogen phosphate TS (1 in 10), methanol and

acetonitrile (6:4:3) to make exactly 20 mL. Confirm that the peak area of irinotecan obtained with 20 μL of this solution is equivalent to 3.5 to 6.5% of that with 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of irinotecan are not less than 6000 and not more than 2.0, respectively.

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 irinotecan is not more than 2.0%.

(3) Optical isomer—Being specified separately when the drug is granted approval based on the Law.

Water *<2.48>* 7.5 – 9.5% (0.1 g, volumetric titration, direct titration).

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

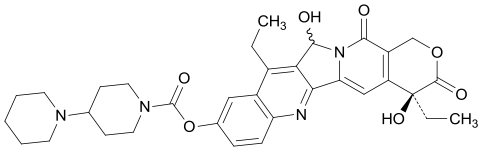
Assay Weigh accurately about 0.44 g of Irinotecan Hydrochloride Hydrate, dissolve in 120 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate *<2.50>* with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
＝31.16 mg of $C_{33}H_{38}N_4O_6$.HCl

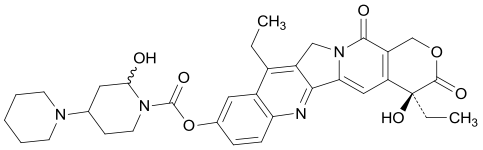
Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Others

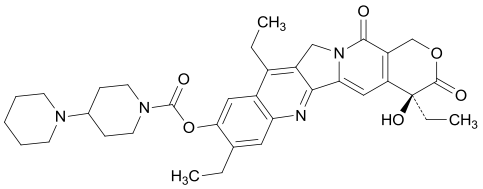
Related substance A:
(4*S*)-4,11-Diethyl-4,12-dihydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-9-yl [1,4'-bipiperidine]-1'-carboxylate



Related substance B:
(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-9-yl 2'-hydroxy-[1,4'-bipiperidine]-1'-carboxylate



Related substance C:
(4*S*)-4,8,11-Triethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-9-yl [1,4'-bipiperidine]-1'-carboxylate



Related substance D:
(4*S*)-4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-9-yl 2'-ethoxy-[1,4'-bipiperidine]-1'-carboxylate