Irinotecan Hydrochloride Injection

イリノテカン塩酸塩注射液

Irinotecan Hydrochloride Injection is an aqueous injection.

It contains not less than 95.0% and not more than 105.0% of the labeled amount of irinotecan hydrochloride hydrate ($C_{33}H_{38}N_4O_6.HCl.3H_2O$: 677.18).

Method of preparation Prepare as directed under Injections, with Irinotecan Hydrochloride Hydrate.

Description Irinotecan Hydrochloride Injection is a clear and pale yellow liquid.

It is gradually decomposed by light.

Identification To a volume of Irinotecan Hydrochloride Injection, equivalent to 20 mg of Irinotecan Hydrochloride Hydrate, add water to make 10 mL. To 1 mL of this solution add water to make 100 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits maxima between 253 nm and 257 nm, between 354 nm and 358 nm, and between 368 nm and 372 nm.

pH Being specified separately when the drug is granted approval based on the Law.

Purity Related substances—To a volume of Irinotecan Hydrochloride Injection, equivalent to 40 mg of Irinotecan Hydrochloride Hydrate, add 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 this 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 25 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 area of related substance IA, having the relative retention time of about 0.3 to irinotecan, obtained from the sample solution is not larger than 1/2 times the peak area of irinotecan from the standard solution, the areas of related substances A and B, having the relative retention time of about 0.8, from the sample solution are not larger than 3/10 times the peak area of irinotecan from the standard solution, the area of related substance IB, having the relative retention time of about 1.3, from the sample solution is not larger than 1/3 times the peak area of irinotecan from the standard solution, the areas of related substances C and D, having the relative retention time of about 1.6, and related substance IC, having the relative retention time of about 2.2, 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 1.5 times the peak area of irinotecan from the standard solution.

Operating conditions—

Proceed as directed in the operating conditions in the Purity (2) under Irinotecan Hydrochloride Hydrate.

System suitability—

Test for required detectability: Pipet 1 mL of the standard 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 20 mL. Confirm that the peak area of irinotecan obtained with 25 μL of this solution is equivalent to 3.5 to 6.5% of that with 25 μL of the standard solution.

System performance: When the procedure is run with 25 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 25 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%.

Bacterial endotoxins *<4.01>* Less than 1.8 EU/mg.

Extractable volume *<6.05>* It meets the requirement.

Foreign insoluble matter *<6.06>* Perform the test according to Method 1: it meets the requirement.

Insoluble particulate matter *<6.07>* It meets the requirement.

Sterility *<4.06>* Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Irinotecan Hydrochloride Injection, equivalent to about 20 mg of irinotecan hydrochloride hydrate ($C_{33}H_{38}N_4O_6.HCl.3H_2O$), and add a mixture of methanol and acetic acid-sodium acetate buffer solution (pH 4.0) (11:9) to make exactly 50 mL. Pipet 10 mL of this solution, add the internal standard solution to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of irinotecan hydrochloride hydrate for assay (separately determine the water *<2.48>* in the same manner as Irinotecan Hydrochloride Hydrate), dissolve in a mixture of methanol and acetic acid-

sodium acetate buffer solution (pH 4.0) (11:9) to make exactly 50 mL. Pipet 10 mL of this solution, add the internal standard solution to make exactly 100 mL, and use this solution as the standard solution. 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 irinotecan to that of the internal standard.

Amount (mg) of irinotecan hydrochloride hydrate ($C_{33}H_{38}N_4O_6.HCl.3H_2O$)
$= M_S \times Q_T / Q_S \times 1.087$

M_S: Amount (mg) of irinotecan hydrochloride hydrate for assay taken, calculated on the anhydrous basis

Internal standard solution—Dissolve 33.3 mg of propyl parahydroxybenzoate in a mixture of methanol and acetic acid-sodium acetate buffer solution (pH 4.0) (11:9) to make 1000 mL.

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 40℃.

Mobile phase: Dissolve 1.01 g of sodium 1-heptanesulfonate in a mixture of methanol and acetic acid-sodium acetate buffer solution (pH 4.0) (11:9) to make 1000 mL.

Flow rate: Adjust so that the retention time of irinotecan 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, irinotecan and the internal standard are eluted in this order with the resolution between these peaks being not less than 6.

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 irinotecan to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Hermetic containers.

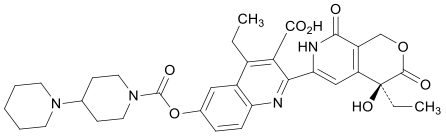
Storage—Light-resistant.

Others

Related substances A, B, C and D: refer to them described in Irinotecan Hydrochloride Hydrate.

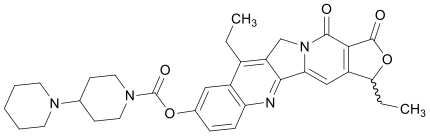
Related substances IA:

6-{[1,4'-Bipiperidine]-1'-carbonyloxy}-4-ethyl-2-[(4*S*)-4-ethyl-4-hydroxy-3,8-dioxo-3,4,7,8-tetrahydro-1*H*-pyrano[3,4-*c*]pyridin-6-yl]quinoline-3-carboxylic acid



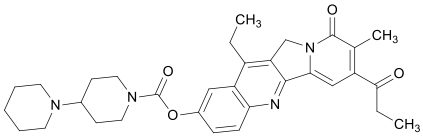
Related substances IB:

3,10-Diethyl-1,13-dioxo-1,3,11,13-tetrahydrofuro[3',4':6,7]indolizino[1,2-*b*]quinolin-8-yl [1,4'-bipiperidine]-1'-carboxylate



Related substances IC:

12-Ethyl-8-methyl-9-oxo-7-propionyl-9,11-dihydroindolizino[1,2-*b*]quinolin-2-yl [1,4'-bipiperidine]-1'-carboxylate



Add the following to 9.41 Reagents, Test Solutions:

Irinotecan hydrochloride hydrate for assay $C_{33}H_{38}N_4O_6.HCl.3H_2O$ [Same as the monograph Irinotecan Hydrochloride Hydrate]