

1 **Irinotecan Hydrochloride Injection**

2 イリノテカン塩酸塩注射液

3

4 Irinotecan Hydrochloride Injection is an aqueous
5 injection.

6 It contains not less than 95.0% and not more than
7 105.0% of the labeled amount of irinotecan hydro-
8 chloride hydrate ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$: 677.18).

9 **Method of preparation** Prepare as directed under Injec-
10 tions, with Irinotecan Hydrochloride Hydrate.

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

13 It is gradually decomposed by light.

14 **Identification** To a volume of Irinotecan Hydrochloride
15 Injection, equivalent to 20 mg of Irinotecan Hydrochloride
16 Hydrate, add water to make 10 mL. To 1 mL of this solution
17 add water to make 100 mL. Determine the absorption spec-
18 trum of this solution as directed under Ultraviolet-visible
19 Spectrophotometry <2.24>: it exhibits maxima between 253
20 nm and 257 nm, between 354 nm and 358 nm, and between
21 368 nm and 372 nm.

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

24 **Purity** Related substances—To a volume of Irinotecan
25 Hydrochloride Injection, equivalent to 40 mg of Irinotecan
26 Hydrochloride Hydrate, add a mixture of diluted 0.1 mol/L
27 potassium dihydrogen phosphate TS (1 in 10), methanol
28 and acetonitrile (6:4:3) and 1 mL of 1 mol/L hydrochloric
29 acid TS to make 20 mL, and use this solution as the sample
30 solution. Pipet 1 mL of this solution, add a mixture of di-
31 luted 0.1 mol/L potassium dihydrogen phosphate TS (1 in
32 10), methanol and acetonitrile (6:4:3) to make exactly 100
33 mL, and use this solution as the standard solution. Perform
34 the test with exactly 25 μ L each of the sample solution and
35 standard solution as directed under Liquid Chromatography
36 <2.01> according to the following conditions. Determine
37 each peak area by the automatic integration method: the
38 area of related substance IA, having the relative retention
39 time of about 0.3 to irinotecan, obtained from the sample
40 solution is not larger than 1/2 times the peak area of iri-
41 notecan from the standard solution, the areas of related sub-
42 stances A and B, having the relative retention time of about
43 0.8, from the sample solution are not larger than 3/10 times
44 the peak area of irinotecan from the standard solution, the
45 area of related substance IB, having the relative retention
46 time of about 1.3, from the sample solution is not larger than
47 1/3 times the peak area of irinotecan from the standard so-
48 lution, the areas of related substances C and D, having the
49 relative retention time of about 1.6, and related substance

50 IC, having the relative retention time of about 2.2, from the
51 sample solution are not larger than 1/5 times the peak area
52 of irinotecan from the standard solution, and the area of the
53 peak other than irinotecan and the peaks mentioned above
54 from the sample solution is not larger than 1/10 times the
55 peak area of irinotecan from the standard solution. Further-
56 more, the total area of the peaks other than irinotecan from
57 the sample solution is not larger than 1.5 times the peak area
58 of irinotecan from the standard solution.

59 *Operating conditions*—

60 Proceed as directed in the operating conditions in the Pu-
61 rity (2) under Irinotecan Hydrochloride Hydrate.

62 *System suitability*—

63 Test for required detectability: Pipet 1 mL of the standard
64 solution, add a mixture of diluted 0.1 mol/L potassium
65 dihydrogen phosphate TS (1 in 10), methanol and
66 acetonitrile (6:4:3) to make exactly 20 mL. Confirm that the
67 peak area of irinotecan obtained with 25 μ L of this solution
68 is equivalent to 3.5 to 6.5% of that with 25 μ L of the
69 standard solution.

70 System performance: When the procedure is run with 25
71 μ L of the standard solution under the above operating
72 conditions, the number of theoretical plates and the
73 symmetry factor of the peak of irinotecan are not less than
74 6000 and not more than 2.0, respectively.

75 System repeatability: When the test is repeated 6 times
76 with 25 μ L of the standard solution under the above
77 operating conditions, the relative standard deviation of the
78 peak area of irinotecan is not more than 2.0%.

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

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

81 **Foreign insoluble matter** <6.06> Perform the test ac-
82 cording to Method 1: it meets the requirement.

83 **Insoluble particulate matter** <6.07> It meets the re-
84 quirement.

85 **Sterility** <4.06> Perform the test according to the Mem-
86 brane filtration method: it meets the requirement.

87 **Assay** Pipet a volume of Irinotecan Hydrochloride Injec-
88 tion, equivalent to about 20 mg of irinotecan hydrochloride
89 hydrate ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$), and add a mixture of
90 methanol and acetic acid-sodium acetate buffer solution
91 (pH 4.0) (11:9) to make exactly 50 mL. Pipet 10 mL of this
92 solution, add the internal standard solution to make exactly
93 100 mL, and use this solution as the sample solution. Sepa-
94 rately, weigh accurately about 20 mg of irinotecan hydro-
95 chloride hydrate for assay (separately determine the water
96 <2.48> in the same manner as Irinotecan Hydrochloride Hy-
97 drate), dissolve in a mixture of methanol and acetic acid-

98 sodium acetate buffer solution (pH 4.0) (11:9) to make ex-
 99 actly 50 mL. Pipet 10 mL of this solution, add the internal
 100 standard solution to make exactly 100 mL, and use this so-
 101 lution as the standard solution. Perform the test with 10 μ L
 102 each of the sample solution and standard solution as di-
 103 rected under Liquid Chromatography <2.01> according to
 104 the following conditions, and calculate the ratios, Q_T and Q_S ,
 105 of the peak area of irinotecan to that of the internal standard.

$$\begin{aligned} & \text{Amount (mg) of irinotecan hydrochloride hydrate} \\ & (\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_6 \cdot \text{HCl} \cdot 3\text{H}_2\text{O}) \\ & = M_S \times Q_T / Q_S \times 1.087 \end{aligned}$$

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

111 *Internal standard solution*— Dissolve 33.3 mg of propyl
 112 parahydroxybenzoate in a mixture of methanol and acetic
 113 acid-sodium acetate buffer solution (pH 4.0) (11:9) to make
 114 1000 mL.

115 *Operating conditions*—

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

118 Column: A stainless steel column 6 mm in inside
 119 diameter and 15 cm in length, packed with
 120 octadecylsilanized silica gel for liquid chromatography (5
 121 μ m in particle diameter).

122 Column temperature: A constant temperature of about
 123 40°C.

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

128 Flow rate: Adjust so that the retention time of irinotecan
 129 is about 7 minutes.

130 *System Suitability*—

131 System performance: When the procedure is run with 10
 132 μ L of the standard solution under the above operating
 133 conditions, irinotecan and the internal standard are eluted in
 134 this order with the resolution between these peaks being not
 135 less than 6.

136 System repeatability: When the test is repeated 6 times
 137 with 10 μ L of the standard solution under the above
 138 operating conditions, the relative standard deviation of the
 139 ratios of the peak area of irinotecan to that of the internal
 140 standard is not more than 1.0%.

141 **Containers and storage** Containers—Hermetic contain-
 142 ers.

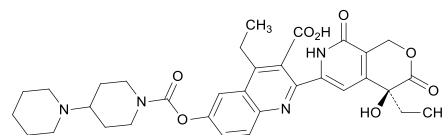
143 Storage—Light-resistant.

144 **Others**

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

147 Related substances IA:

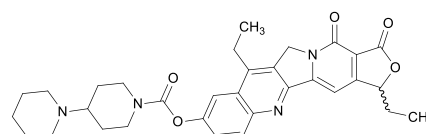
148 6-{{[1,4'-Bipiperidine]-1'-carboxyloxy}-4-ethyl-2-[(4S)-4-
 149 ethyl-4-hydroxy-3,8-dioxo-3,4,7,8-tetrahydro-1H-pyrano
 150 [3,4-c]pyridin-6-yl]quinoline-3-carboxylic acid



151

152 Related substances IB:

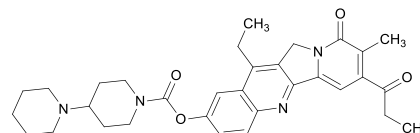
153 3,10-Diethyl-1,13-dioxo-1,3,11,13-tetrahydrofuro
 154 [3',4':6,7]indolizino[1,2-*b*]quinolin-8-yl [1,4'-bipiperidine]-
 155 1'-carboxylate



156

157 Related substances IC:

158 12-Ethyl-8-methyl-9-oxo-7-propionyl-9,11-dihydroin-
 159 dolizino
 160 [1,2-*b*]quinolin-2-yl [1,4'-bipiperidine]-1'-carboxylate



161

162

163 **Add the following to 9.41 Reagents,**
 164 **Test Solutions:**

165 **Irinotecan hydrochloride hydrate for assay**
 166 $\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_6 \cdot \text{HCl} \cdot 3\text{H}_2\text{O}$ [Same as the monograph Irinotecan
 167 Hydrochloride Hydrate]