Doripenem for Injection

注射用ドリペネム

Doripenem for Injection is a preparation for injection, which is dissolved before use.

It contains not less than 95.0% and not more than 105.0% of the labeled potency of doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50).

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

Description Doripenem for Injection occurs as a white to pale yellow-brown-white crystalline powder.

Identification Proceed as directed in the Identification (2) under Doripenem Hydrate.

pH *<2.54>* Dissolve an amount of Doripenem for Injection, equivalent to 0.3 g (potency) of Doripenem Hydrate, in 30 mL of water: the pH of the solution is between 4.5 and 6.0.

Purity **(1)** Clarity and color of solution–Dissolve an amount of Doripenem for Injection, equivalent to 0.2 g (potency) of Doripenem Hydrate in 20 mL of water, and perform the test with this solution as directed in the Purity (1) under Doripenem Hydrate.

(2) Related substances－(i) Dissolve an amount of Doripenem for Injection, equivalent to 20 mg (potency) of Doripenem Hydrate, in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water 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, and determine each peak area by the automatic integration method: the area of the peak other than doripenem and the peak, having the relative retention time of about 2.1 to doripenem, related substance A having the relative retention time of about 2.2, related substance B having the relative retention time of about 2.5 and related substance C having the relative retention time of about 3.2, obtained from the sample solution is not larger than 1/10 times the peak area of doripenem from the standard solution, and the total area of the peaks, other than doripenem and the peaks mentioned above, from the sample solution is not larger than 1/2 times the peak area of doripenem from the standard solution.

Operating conditions－

Proceed as directed in the operating conditions in the Purity (3) (i) under Doripenem Hydrate.

System suitability－

Test for required detectability: Pipet 2.5 mL of the standard solution, and add water to make exactly 50 mL. Confirm that the peak area of doripenem 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 doripenem are not less than 5000 and not more than 1.3, respectively.

System repeatability: When the test is repeated 3 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 0.95%.

(ii) Dissolve an amount of Doripenem for Injection, equivalent to about 20 mg (potency) of Doripenem Hydrate, in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water 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 area of related substance D, having the relative retention time of about 0.5 to doripenem, obtained from the sample solution is not larger than the peak area of doripenem from the standard solution.

Operating conditions－

Proceed as directed in the operating conditions in the Purity (3) (ii) under Doripenem Hydrate.

System performance: To 1 mL of the sample solution add 1 mL of 0.1 mol/L hydrochloric acid TS, allow to stand at 25±5℃ for 15 minutes, and add water to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, related substance D and doripenem are eluted in this order with the resolution between these peaks being not less than 5. The number of theoretical plates and the symmetry factor of the peak of related substance D are not less than 300 and 0.7 to 1.3, respectively, and those of the peak of doripenem are not less than 5000 and 0.7 to 1.3, 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 doripenem is not more than 2.0%.

Water *<2.48>* 4.0 – 5.0% (0.3 g, volumetric titration, back titration).

Bacterial endotoxins *<4.01>* Less than 0.25 EU/mg (potency).

Uniformity of dosage units *<6.02>* It meets the requirement of the Mass variation test.

Foreign insoluble matter *<6.06>* Perform the test according to Method 2: 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 Weigh accurately the mass of the contents of not less than 10 containers of Doripenem for Injection. Weigh accurately an amount of the contents, equivalent to about 25 mg (potency) of Doripenem Hydrate, dissolve in water to make exactly 200 mL, and use this solution as the sample solution. Separately, weigh accurately about 25 mg (potency) of Doripenem RS (separately determine the water *<2.48>* in the same manner as Doripenem Hydrate), dissolve in water to make exactly 200 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay under Doripenem Hydrate.

Amount [μg (potency)] of doripenem ($C_{15}H_{24}N_4O_6S_2$)
$= M_S \times A_T / A_S \times 1000$

M_S: Amount [mg (potency)] of Doripenem RS taken, calculated on the anhydrous basis

Containers and storage Containers — Hermetic containers. Plastic containers for aqueous injections may be used.

Others

Related substances A, B, C and D: Refer to them described in Doripenem Hydrate.

Add the following to 9.01 Reference Standards (1):

Doripenem RS