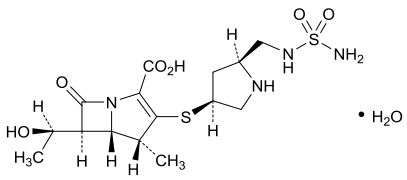
Doripenem Hydrate

ドリペネム水和物



$C_{15}H_{24}N_4O_6S_2.H_2O$: 438.52

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-{(3*S*,5*S*-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate

[*364622-82-2*]

Doripenem Hydrate contains not less than 970 μg (potency) and not more than 1020 μg (potency) of doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50) per mg, calculated on the anhydrous basis. The potency of Doripenem Hydrate is expressed as mass (potency) of doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50).

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

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

It is gradually colored to pale yellow-brown-white by light.

Identification **(1)** Determine the absorption spectrum of a solution of Doripenem Hydrate (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Doripenem 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 Doripenem Hydrate 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 Doripenem RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation *<2.49>* $[\alpha]_D^{20}$: + 33 – + 38° (0.25 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH *<2.54>* Dissolve 0.3 g 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 0.2 g of Doripenem Hydrate in 20 mL of water, and perform the test with this solution as directed under Turbidity Measurement *<2.61>*: the solution is clear. Perform the test with this solution according to Method 2 under Methods for Color Matching *<2.65>*: the solution is not more colored than Matching Fluid Y4.

(2) Heavy metals *<1.07>*—Moisten 1.0 g of Doripenem Hydrate with sulfuric acid, cover loosely, and heat gently to carbonize. Then proceed according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances (i)—Dissolve 20 mg 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 areas of related substance A, having the relative retention time of about 2.2 to doripenem, 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, are not larger than 1/10 times the peak area of doripenem from the standard solution, and the area of the peak other than doripenem, the peaks mentioned above and the peak having the relative retention time of about 2.1, from the sample solution, is not larger than 1/20 times the peak area of doripenem from the standard solution. Furthermore, the total area of the peaks other than doripenem and the peak having the relative retention time of about 2.1 from the sample solution is not larger than 1/2 times the peak area of doripenem from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4.6 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 30℃.

Mobile phase A: Dissolve 2.04 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 5.6 – 5.7 with a solution prepared by dissolving 2.61 g of potassium dihydrogen phosphate in water to make 1000 mL. To 970 mL of this solution add 30 mL of acetonitrile.

Mobile phase B: Dissolve 2.04 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust to pH 5.6 - 5.7 with a solution prepared by dissolving 2.61 g of potassium dihydrogen phosphate in water to make 1000 mL. To 700 mL of this solution add 300 mL of acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 15	100	0
15 – 45	100 → 50	0 → 50
45 – 50	50 → 0	50 → 100
50 – 55	0	100

Flow rate: 1.0 mL per minute.

Time span of measurement: For 55 minutes after injection, beginning after the peak having the relative retention time of about 0.2 to doripenem.

System suitability—

Test for required detectability: Pipet 1.5 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 2.1 to 3.9% 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 20 mg of Doripenem Hydrate in 10 mL of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and 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 2/5 times the peak area of doripenem from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecyl-strong anion exchange group silanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase: To 9 mL of phosphoric acid add 200 mL of water, add 20 mL of triethylamine, and add water to make 2000 mL. Adjust to pH 5.7 – 5.9 with phosphoric acid. To 950 mL of this solution add 50 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of doripenem is about 10 minutes.

System suitability—

Test for required detectability: Pipet 2 mL of the standard solution, and add water to make exactly 20 mL. Confirm that the peak area of doripenem obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

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%.

(iii) Dissolve 20 mg 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 areas of the peaks, having the relative retention time of about 1.8, about 2.2 and about 2.3 to doripenem, obtained from the sample solution are not larger than 1/20, 7/100 and 1/20 times the peak area of doripenem from the standard solution, respectively.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsi-

lanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 30℃.

Mobile phase A: To 11 mL of perchloric acid add water to make 500 mL. To 100 mL of this solution add water to make 1000 mL. To 600 mL of this solution add 100 mL of water, and adjust to pH 1.9 – 2.0 with a solution prepared by adding water to 2.81 g of sodium perchlorate monohydrate to make 1000 mL. To 900 mL of this solution add 100 mL of acetonitrile.

Mobile phase B: To 11 mL of perchloric acid add water to make 500 mL. To 100 mL of this solution add water to make 1000 mL. To 600 mL of this solution add 100 mL of water, and adjust to pH 1.9 – 2.0 with a solution prepared by adding water to 2.81 g of sodium perchlorate monohydrate to make 1000 mL. To 300 mL of this solution add 200 mL of acetonitrile.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 25	100	0
25 – 55	100 → 0	0 → 100
55 – 60	0	100

Flow rate: 0.8 mL per minute.

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 15,000 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%.

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

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

Assay Weigh accurately amounts of Doripenem Hydrate and Doripenem RS (separately determine the water <*2.48*> in the same manner as Doripenem Hydrate), equivalent to about 25 mg (potency), dissolve each in water to make exactly 200 mL, and use these solutions as the sample solution and the standard solution, respectively. 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 determine the peak areas, A_T and A_S, of doripenem in each solution.

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

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 300 nm).

Column: A stainless steel column 4.6 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 25℃.

Mobile phase: Adjust the pH of 90 mL of 0.02 mol/L potassium dihydrogen phosphate to pH 5.6 – 5.7 with a solution prepared by dissolving 3.48 g of dipotassium hydrogen phosphate in water to make 1000 mL. To 100 mL of this solution add water to make exactly 1000 mL. To 970 mL of this solution add 30 mL of acetonitrile.

Flow rate: Adjust so that the retention time of doripenem is about 15 minutes.

System suitability—

System performance: When the procedure is run with 10 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 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of doripenem is not more than 1.0%.

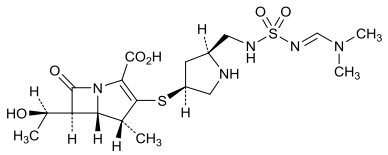
Containers and storage Containers—Tight containers.

Storage—At a temperature between 2℃ and 8℃.

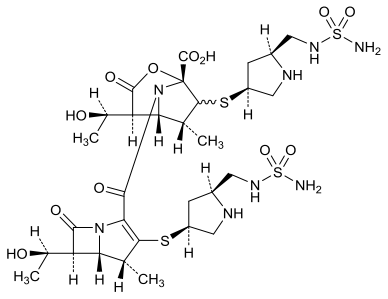
Others

Related substance A:

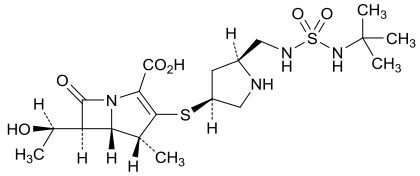
(4*R*,5*S*,6*S*)-3-{(3*S*,5*S*)-5-[({*N*-[*E*-(Dimethylamino)methylene]sulfamoyl}amino)methyl]pyrrolidin-3-ylsulfanyl}-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid



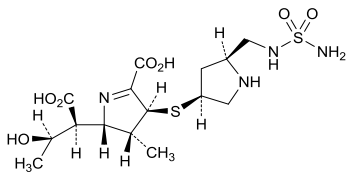
Related substance B:
(1*S*,4*S*,5*S*,6*R*)-4-[(1*R*)-1-Hydroxyethyl]-8-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-{(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-1-azabicyclo[3.2.0]hepta-2-ene-2-carbonyl]-6-methyl-3-oxo-7-{(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-2-oxa-8-azabicyclo[3.2.1]octane-1-carboxylic acid



Related substance C:
(4*R*,5*S*,6*S*)-3-{(3*S*,5*S*)-5-[({*N*-(1,1-Dimethylethyl)sulfamoyl}amino)methyl]pyrrolidin-3-ylsulfanyl}-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid



Related substance D:
(2*S*,3*R*,4*S*)-2-[(1*S*,2*R*)-1-Carboxy-2-hydroxypropyl]-3-methyl-4-[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl}-3,4-dihydro-2*H*-pyrrole-5-carboxylic acid



Add the following to 9.01 Reference Standards (1):

Doripenem RS

Add the following to 9.42 Solid Supports/Column Packings for Chromatography:

Octadecyl-strong anion exchange group silanized silica gel for liquid chromatography Prepared for liquid chromatography.