lute hydrochloric acid and 4 mL of water, add 3 drops of sodium nitrite TS under ice-cooling, shake, and allow to stand for 2 minutes. Then add 1 mL of ammonium amidosulfate TS, shake well, and allow to stand for 1 minute, and add 1 mL of *N,N*-diethyl-*N'*-1-naphthylethylenediamine oxalate TS: a purple color develops.

(3) Determine the absorption spectra of solutions of Cefditoren Pivoxil and Cefditoren Pivoxil Reference Standard in methanol (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the spectrum of a solution of Cefditoren Pivoxil in deuterated chloroform for nuclear magnetic resonance spectroscopy (1 in 50), using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound, as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H): it exhibits single signals A, B and C, at around δ 1.1 ppm, at around δ 2.4 ppm and at around δ 4.0 ppm, double signals D and E, at around δ 6.4 ppm and at around δ 6.7 ppm, and a single signal F at around δ 8.6 ppm. The ratio of integrated intensity of each signal A:B:C:D:E:F, is about 9:3:3:1:1:1.

Absorbance $E^{1\%}_{1\,cm}$ (231 nm): 340 - 360 (0.05 g, methanol, 2500 mL).

Optical rotation $[\alpha]^{20}_D$: −45 - −52° (0.05 g, methanol, 10 mL, 100 mm).

Purity **(1)** Heavy metals—Proceed with 2.0 g of Cefditoren Pivoxil 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—Being specified separately.

(3) Residual solvents—Being specified separately.

Water Not more than 1.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition Being specified separately.

Assay Weigh accurately an amount of Cefditoren Pivoxil and Cefditoren Pivoxil Reference Standard, equivalent to about 0.04 g (potency), dissolve in 40 mL of acetonitrile, add exactly 10 mL each of the internal standard solution, and add acetonitrile to make 100 mL, and use these solutions as the sample solution and the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cefditoren pivoxil to that of the internal standard.

$$\text{Amount [}\mu\text{g (potency)] of cefditoren } (C_{19}H_{18}N_6O_5S_3) = \text{amount [mg (potency)] of Cefditoren Pivoxil Reference Standard} \times \frac{Q_T}{Q_S} \times 1000$$

Internal standard solution—A solution of propyl *p*-hydroxybenzoate in acetonitrile (1 in 200).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 230 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 25°C.

Mobile phase: Dissolve 1.58 g of ammonium formate in 900 mL of water, adjust to pH 6.0 with diluted formic acid (1 in 250), and add water to make 1000 mL. To 450 mL of this solution add 275 mL of acetonitrile and 275 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefditoren pivoxil 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 internal standard and cefditoren pivoxil are eluted in this order with the resolution between these peaks being not less than 5.

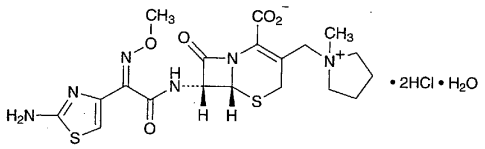
System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of cefditoren pivoxil to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cefepime Dihydrochloride

塩酸セフェピム



$C_{19}H_{24}N_6O_5S_2.2HCl.H_2O$: 571.50

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetylamino]-3-(1-methylpyrrolidinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate dihydrochloride monohydrate

[*123171-59-5*]

Cefepime Dihydrochloride contains not less than 810 μg (potency) per mg, calculated on the anhydrous basis. The potency of Cefepime Dihydrochloride is expressed as mass (potency) of cefepime ($C_{19}H_{24}N_6O_5S_2$: 480.56).

Description Cefepime Dihydrochloride occurs as a white to yellowish white, crystals or crystalline powder.

It is freely soluble in water and in methanol, and slightly soluble in ethanol (95).

Identification **(1)** Dissolve 0.02 g of Cefepime Dihydrochloride in 2 mL of water, add 1 mL of a solution of hydroxylammonium chloride (1 in 10) and 2 mL of sodium hydroxide TS, allow to stand for 5 minutes, then add 3 mL of 1 mol/L hydrochloric acid TS and 3 drops of iron (III) chloride TS: a red-brown color develops.

(2) Determine the absorption spectra of solutions of Cefepime Dihydrochloride and Cefepime Dihydrochloride Reference Standard (1 in 20,000) as directed under the

Ultraviolet-visible Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectra of Cefepime Dihydrochloride and Cefepime Dihydrochloride Reference Standard as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wave numbers.

(4) Determine the spectrum of a solution of Cefepime Dihydrochloride in heavy water for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H), using sodium 3-trimethylsilylpropionate-d_4 for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits single signals, A and B, at around δ 3.1 ppm and at around δ 7.2 ppm, respectively, and the ratio of integrated intensity of each signal, A:B, is about 3:1.

(5) Dissolve 0.015 g of Cefepime Dihydrochloride in 5 mL of water, and add 2 drops of silver nitrate TS: a white turbidity is produced.

Absorbance $E_{1\,cm}^{1\%}$ (259 nm): 310 - 340 (0.05 g calculated on the anhydrous basis, water, 1000 mL).

Optical rotation $[\alpha]_D^{20}$: +39 - +47° (0.06 g calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 0.1 g of Cefepime Dihydrochloride in 10 mL of water: the pH of this solution is between 1.6 and 2.1.

Purity **(1)** Clarity and color of solution—Being specified separately.

(2) Heavy metals—Proceed with 1.0 g of Cefepime Dihydrochloride 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) *N*-Methylpyrrolidine—Weigh accurately an amount of Cefepime Dihydrochloride equivalent to about 0.08 g (potency), dissolve in diluted nitric acid (2 in 3125) to make exactly 10 mL, and use this solution as the sample solution. Separately, put 30 mL of water in a 100-mL volumetric flask, weigh accurately the mass of flask, then add about 0.125 g of *N*-methylpyrrolidine, weigh accurately the mass of the flask again, and add water to make exactly 100 mL. Pipet 4 mL of this solution, add diluted nitric acid (2 in 3125) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 100 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of *N*-methylpyrrolidine by the automatic integration method. Calculate the amount of *N*-methylpyrrolidine per 1 mg (potency) of Cefepime Dihydrochloride by the following equation: not more than 0.5%. The sample solution must be tested within 20 minutes after preparation.

$$\text{Amount (\%) of } N\text{-methylpyrrolidine} = \frac{\text{amount (mg) of } N\text{-methylpyrrolidine taken} \times f}{\text{amount [mg (potency)] of sample taken}} \times \frac{A_T}{A_S} \times \frac{4}{1000}$$

f: Purity (%) of *N*-methylpyrrolidine

Operating conditions—

Detector: An electric conductivity detector

Column: A plastic tube 4.6 mm in inside diameter and 5 cm in length, packed with hydrophilic silica gel for liquid chromatography carrying sulfonic acid groups having the exchange capacity of about 0.3 meq per g (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: To 990 mL of diluted nitric acid (2 in 3125) add 10 mL of acetonitrile.

Flow rate: 1.0 mL per minute.

System suitability—

System performance: To 20 mL of a solution of sodium chloride (3 in 1000) add 0.125 g of *N*-methylpyrrolidine, and add water to make 100 mL. To 4 mL of this solution add diluted nitric acid (2 in 3125) to make 100 mL. When the procedure is run with 100 μL of this solution under the above operating conditions, sodium and *N*-methylpyrrolidine are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 5 times with 100 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of *N*-methylpyrrolidine is not more than 4.0%.

(4) Related substances—Dissolve about 0.1 g of Cefepime Dihydrochloride in the mobile phase A to make 50 mL, and use this solution as the sample solution. Perform the test with 5 μL of the sample solution as directed under the Liquid Chromatography according to the following conditions, and determine the area of each peak by the automatic integration method. Calculate the total of the peak areas other than cefepime: not more than 0.5%.

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 (10 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase A: Dissolve 0.57 g of ammonium dihydrogenphosphate in 1000 mL of water.

Mobile phase B: Acetonitrile

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

Time after injection of the sample (min)	Mobile phase A (%)	Mobile phase B (%)
0–25	100→75	0→25

Flow rate: Adjust the flow rate so that the retention time of cefepime is about 9.5 minutes.

Time span of measurement: About 2.5 times as long as the retention time of cefepime.

System suitability—

Test for required detection: To 1 mL of the sample solution add the mobile phase A to make 10 mL, and use this solution as the solution for system suitability test. To 1 mL of the solution for system suitability test add the mobile phase A to make 10 mL, and use this solution as the solution for

test for required detection. Pipet 1 mL of the solution for test for required detection, add the mobile phase A to make exactly 10 mL. Conform that the peak area of cefepime obtained from 5 μL of this solution is equivalent to 7 to 13% of that of cefepime obtained from 5 μL of the solution for test for required detection.

System performance: When the procedure is run with 5 μL of the solution for system suitability test under the above operating conditions, the number of theoretical steps of the peak of cefepime is not less than 6000 steps.

System repeatability: When the test is repeated 3 times with 5 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak areas of cefepime is not more than 2.0%.

Water Not less than 3.0% and not more than 4.5% (Weigh accurately about 0.05 g, and add exactly 2 mL of methanol for water determination to dissolve. Use exactly 0.5 mL of this solution as the test solution; coulometric titration).

Residue on ignition Not more than 0.1% (1 g).

Bacterial endotoxins Less than 0.04 EU/mg (potency).

Assay Weigh accurately an amount of Cefepime Dihydrochloride and Cefepime Dihydrochloride Reference Standard, equivalent to about 0.06 g (potency), dissolve in the mobile phase to make exactly 500 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefepime of each solution.

Amount [μg (potency)] of cefepime ($C_{19}H_{24}N_6O_5S_2$)
= amount [mg (potency)] of Cefepime Dihydrochloride Reference Standard $\times \frac{A_T}{A_S} \times 1000$

Operating conditions—

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

Column: A stainless steel column 3.9 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

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

Mobile phase: Adjust a solution of sodium 1-pentanesulfonate (261 in 100,000) to pH 3.0 with acetic acid (100), then adjust this solution to pH 4.0 with a solution of potassium hydroxide (13 in 20). To 950 mL of this solution add 50 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefepime is about 8 minutes.

System suitability—

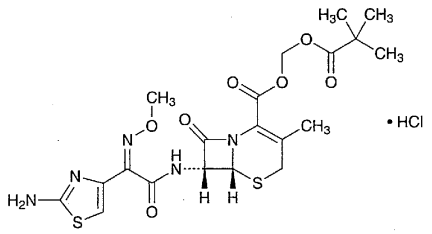
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical steps of the peak of cefepime is not less than 1500 steps.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of cefepime is not more than 2.0%.

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

Cefetamet Pivoxil Hydrochloride

塩酸セフェタメト ピボキシル



$C_{20}H_{25}N_5O_7S_2.HCl$: 548.03

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetylamino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monohydrochloride [*111696-23-2*]

Cefetamet Pivoxil Hydrochloride contains not less than 653 μg (potency) per mg, calculated on the anhydrous basis. The potency of Cefetamet Pivoxil Hydrochloride is expressed as mass (potency) of cefetamet ($C_{14}H_{15}N_5O_5S_2$: 397.43).

Description Cefetamet Pivoxil Hydrochloride occurs as a white to light yellowish white crystalline powder.

It is very soluble in *N,N*-dimethylformamide and in methanol, and freely soluble in ethanol (95), and practically insoluble in water.

Identification **(1)** Dissolve 0.01 g of Cefetamet Pivoxil Hydrochloride in 2 mL of diluted methanol (1 in 2), add 3 mL of hydroxylammonium chloride-ethanol TS, allow to stand for 5 minutes, then add 1 mL of acidic ammonium iron (III) sulfate TS, and shake: a red-brown color develops.

(2) Determine the absorption spectra of solutions of Cefetamet Pivoxil Hydrochloride and Cefetamet Pivoxil Hydrochloride Reference Standard in 0.1 mol/L hydrochloric acid TS (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectra of Cefetamet Pivoxil Hydrochloride and Cefetamet Pivoxil Hydrochloride Reference Standard as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare these spectra: both spectra exhibit similar intensities of absorption at the same wave numbers.

(4) Determine the spectrum of a solution of Cefetamet Pivoxil Hydrochloride in deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy (1 in 20) as directed under the Nuclear Magnetic Resonance Spectroscopy (^1H), using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits single signals, A, B, C and D, at around δ 1.2 ppm, at around δ 2.0 ppm, at around δ 3.9 ppm and at around δ 6.9 ppm, respectively, and the ratio of integrated