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 cefsulodin is not more than 1.0%.

Water Not more than 5.0% (1 g, volumetric titration, direct titration, avoiding moisture absorption of the sample, using a mixture of formamide for water determination and methanol for water determination (2:1) instead of methanol for water determination).

Assay Weigh accurately an amount of Cefsulodin Sodium and Cefsulodin Sodium Reference Standard, equivalent to about 0.1 g (potency), dissolve each in water to make exactly 50 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 peak areas, A_T and A_S, of cefsulodin of each solution.

$$\text{Amount [}\mu\text{g (potency)] of } C_{22}H_{20}N_4O_8S_2 = \text{amount [mg (potency)] of Cefsulodin Sodium Reference Standard} \times \frac{A_T}{A_S} \times 1000$$

Operating conditions—

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

Column: A stainless steel column 4 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°C.

Mobile phase: A mixture of a solution of ammonium sulfate (1 in 100) and acetonitrile (97:3).

Flow rate: Adjust the flow rate so that the retention time of cefsulodin is about 9 minutes.

System suitability—

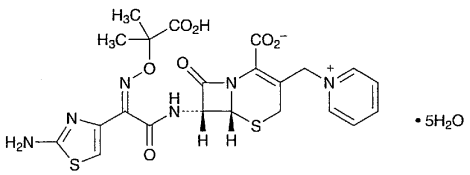
System performance: Dissolve 0.040 g of isonicotinic acid amide in 25 mL of the standard solution. When the procedure is run with 10 μL of this solution under the above operating conditions, isonicotinic acid amide and cefsulodin are eluted in this order with the resolution between these peaks being 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 peak areas of cefsulodin is not more than 1.0%.

Containers and storage Containers—Hermetic containers.

Ceftazidime

セフタジジム



$C_{22}H_{22}N_6O_7S_2.5H_2O$: 636.65

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetylamino]-3-(pyridinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate [*72558-82-8*]

Ceftazidime contains not less than 950 μg (potency) per mg, calculated on the dried basis. The potency of Ceftazidime is expressed as mass (potency) of ceftazidime ($C_{22}H_{22}N_6O_7S_2$: 546.58).

Description Ceftazidime occurs as a white to light yellowish white crystalline powder.

It is slightly soluble in water, and very slightly soluble in acetonitrile and in ethanol (95).

Identification **(1)** Determine the absorption spectrum of a solution of Ceftazidime in phosphate buffer solution, pH 6.0 (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Ceftazidime Reference Standard: both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared absorption spectrum of Ceftazidime as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Ceftazidime Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) To 0.05 g of Ceftazidime add 5 mg of dried sodium carbonate, and add 0.5 mL of heavy water for nuclear magnetic resonance spectroscopy to dissolve. Determine the spectrum of this solution as directed under the Nuclear Magnetic Resonance Spectroscopy (^1H), using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits single signals, A and B, at around δ 1.5 ppm and at around δ 6.9 ppm, and a multiple signal C between δ 7.9 ppm and δ 9.2 ppm. The ratio of integrated intensity of each signal, A:B:C, is about 6:1:5.

Optical rotation $[\alpha]_D^{20}$: −28 – −34° (0.5 g calculated on the dried bases, phosphate buffer solution, pH 6.0, 100 mL, 100 mm).

pH Dissolve 0.5 g of Ceftazidime in 100 mL of water: the pH of the solution is between 3.0 and 4.0.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Ceftazidime in 10 mL of a solution obtained by dissolving 5 g of anhydrous disodium hydrogenphosphate and 1 g of potassium dihydrogenphosphate in water to make 100 mL: the solution is clear, and its absorbance at 420 nm is not more than 0.20.

(2) Heavy metals—Proceed with 1.0 g of Ceftazidime 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) Arsenic—Prepare the test solution with 1.0 g of Ceftazidime according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances 1) Trityl-*t*-butyl substance and *t*-butyl substance—Dissolve 0.10 g of Ceftazidime in 2 mL of diluted disodium hydrogenphosphate TS (1 in 3), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add diluted disodium hydrogenphosphate TS

(1 in 3) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 2 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop with a mixture of *n*-butyl acetate, acetic acid (100), acetate buffer solution, pH 4.5 and 1-butanol (16:16:13:3) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots which appear upper in position than the principal spot from the sample solution are not more intense than the spot from the standard solution.

2) Other related substances—Dissolve 0.02 g of Ceftazidime in 10 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the areas of each peak by the automatic integration method: each peak area other than ceftazidime from the sample solution is not more than that of ceftazidime from the standard solution, and the total of peak areas other than ceftazidime from the sample solution is not more than 5 times of the peak area of ceftazidime from the standard solution.

Operating conditions—

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

Column: A stainless steel column 4.6 mm in inside diameter and 20 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 5.0 g of ammonium dihydrogenphosphate in 750 mL of water, adjust to pH 3.5 with phosphoric acid, and add water to make 870 mL. To this solution add 130 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftazidime is about 4 minutes.

Time span of measurement: About 3 times as long as the retention time of ceftazidime after the solvent peak.

System suitability—

Test for required detection: Pipet 1 mL of the standard solution, add the mobile phase to make exactly 5 mL, and confirm that the peak area of ceftazidime obtained from 5 μL of this solution is equivalent to 15 to 25% of that of ceftazidime obtained from 5 μL of the standard solution.

System performance: Dissolve about 0.01 g each of Ceftazidime and acetanilide in 20 mL of the mobile phase. When the procedure is run with 5 μL of this solution under the above operating conditions, ceftazidime and acetanilide are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of ceftazidime is not more than 2.0%.

(5) Free pyridine—Weigh accurately about 0.05 g of Ceftazidime, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.1 g of pyridine, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase 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 the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak height, H_T and H_S, of pyridine of each solution: the amount of free pyridine is not more than 0.3%.

$$\text{Amount (mg) of free pyridine} = \text{amount (mg) of pyridine} \times \frac{H_T}{H_S} \times \frac{1}{10{,}000}$$

Operating conditions—

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

Column: A stainless steel column 4.6 mm in inside diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase: Dissolve 2.88 g of ammonium dihydrogenphosphate in 500 mL of water, add 300 mL of acetonitrile and water to make 1000 mL, and adjust to pH 7.0 with ammonia solution (28).

Flow rate: Adjust the flow rate so that the retention time of pyridine is about 4 minutes.

System suitability—

Test for required detection: Confirm that the peak height of pyridine obtained from 10 μL of the standard solution is equivalent to 50% of the full scale.

System performance: Dissolve 5 mg of Ceftazidime in 100 mL of a solution of pyridine in the mobile phase (1 in 20,000). When the procedure is run with 10 μL of this solution under the above operating conditions, ceftazidime and pyridine are eluted in this order with the resolution between these peaks being not less than 9.

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 heights of pyridine is not more than 5.0%.

Loss on dryness Not less than 13.0% and not more than 15.0% (0.1 g, in vacuum not exceeding 0.67 kPa, 60°C, 3 hours).

Assay Weigh accurately an amount of Ceftazidime and Ceftazidime Reference Standard, equivalent to about 0.1 g (potency), and dissolve each in 0.05 mol/L phosphate buffer solution, pH 7.0 to make exactly 100 mL. Pipet 10 mL each of these solutions, add exactly 5 mL of the internal standard solution, then add 0.05 mol/L phosphate buffer solution, pH 7.0 to make 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 5 μL each of these solutions 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 ceftazidime to that of the internal standard of each solution.

$$\text{Amount [μg (potency)] of } C_{22}H_{22}N_6O_7S_2 = \text{amount [mg (potency)] of Ceftazidime Reference Standard} \times \frac{Q_T}{Q_S} \times 1000$$

Internal standard solution—A solution of dimedon in 0.05 mol/L phosphate buffer solution, pH 7.0 (11 in 10,000).

Operating conditions—

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

Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with hexasilanized silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase: Dissolve 4.26 g of anhydrous disodium hydrogenphosphate and 2.72 g of potassium dihydrogenphosphate in 980 mL of water, and add 20 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftazidime is about 4 minutes.

System suitability—

System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, the internal standard and ceftazidime are eluted in this order with the resolution between these peaks being not less than 3.

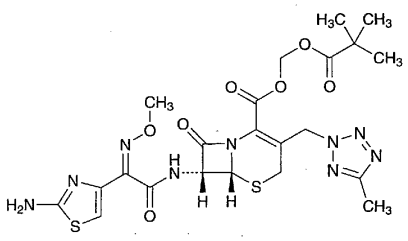
System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of ceftazidime to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cefteram Pivoxil

セフテラムピボキシル



$C_{22}H_{27}N_9O_7S_2$: 593.64

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetylamino]-3-(5-methyl-2*H*-tetrazol-2-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [*82547-58-8*, Cefteram]

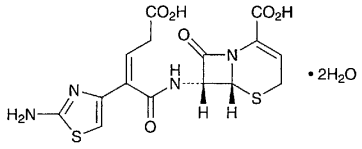
Cefteram Pivoxil conforms to the requirements of Cefteram Pivoxil in the Requirements for Antibiotic Products of Japan.

Description Cefteram Pivoxil occurs as a white to yellowish white powder. It has a bitter taste.

It is freely soluble in methanol and in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

Ceftibuten

セフチブテン



$C_{15}H_{14}N_4O_6S_2.2H_2O$: 446.46

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-4-carboxybut-2-enoylamino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid dihydrate [*118081-34-8*]

Ceftibuten contains not less than 900 μg (potency) per mg, calculated on the anhydrous basis. The potency of Ceftibuten is expressed as mass (potency) of ceftibuten ($C_{15}H_{14}N_4O_6S_2$: 410.42).

Description Ceftibuten occurs as a white to pale yellowish white crystalline powder and has a slight, characteristic odor.

It is freely soluble in *N,N*-dimethylformamide and in dimethyl sulfoxide, and practically insoluble in water, in ethanol (95) and in diethyl ether.

Identification (1) Determine the absorption spectrum of a solution of Ceftibuten in 0.1 mol/L phosphate buffer solution for ceftibuten, pH 8.0 (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 261 nm and 265 nm.

(2) Determine the infrared absorption spectrum of Ceftibuten as directed in the paste method under the Infrared Spectrophotometry: it exhibits absorption at the wave numbers of about 3249 cm^{-1}, 1772 cm^{-1}, 1700 cm^{-1}, 1651 cm^{-1} and 1544 cm^{-1}.

(3) Determine the spectrum of a solution of Ceftibuten in deuterated dimethyl sulfoxide for nuclear magnetic resonance spectroscopy (1 in 30), using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound, as directed under the Nuclear Magnetic Resonance Spectroscopy (^1H): it exhibits double signals A and B, at around δ 3.2 ppm and at around δ 5.1 ppm, a quartet signal C, at around δ 5.8 ppm, and a single signal D, at around δ 6.3 ppm. The ratio of integrated intensity of each signal except the signal at around δ 3.2 ppm, B:C:D is about 1:1:1.

Absorbance $E^{1\%}_{1\,cm}$ (263 nm): 320 – 345 (0.02 g calculated on the anhydrous basis, 0.1 mol/L phosphate buffer solution for ceftibuten, pH 8.0, 1000 mL).

Optical rotation $[\alpha]^{20}_D$: +135 – +155° (0.3 g calculated on the anhydrous basis, 0.1 mol/L phosphate buffer solution for ceftibuten, pH 8.0, 50 mL, 100 mm).

Purity (1) Heavy metals—Proceed with 2.0 g of Ceftibuten 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.

Water Not less than 8.0% and not more than 13.0% (0.2 g, volumetric titration, direct titration. Use a mixture of