Cefotiam Hydrochloride

セフォチアム塩酸塩

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\text{C}_{18}\text{H}_{23}\text{N}_{9}\text{O}_{4}\text{S}_{3}.2\text{HCl}: 598.55
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(6R,7R)-7-[(2-Aminothiazol-4-yl)acetylamino]-3-[(1-dimethylaminoethyl)1H-tetrazol-5-ylsulfonylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid dihydrochloride

[66309-69-1]

Cefotiam Hydrochloride contains not less than 810 \(\mu g\) (potency) and not more than 890 \(\mu g\) (potency) per mg, calculated on the anhydrous basis. The potency of Cefotiam Hydrochloride is expressed as mass (potency) of cefotiam (\(\text{C}_{18}\text{H}_{23}\text{N}_{9}\text{O}_{4}\text{S}_{3}: 525.63\)).

**Description** Cefotiam Hydrochloride occurs as white to light yellow, crystals or crystalline powder. It is freely soluble in water, in methanol and in formamide, slightly soluble in ethanol (95), and practically insoluble in acetonitrile.

**Identification**

1. Determine the absorption spectrum of a solution of Cefotiam Hydrochloride (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Cefotiam Hydrochloride 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 Cefotiam Hydrochloride as directed in the potassium chloride disk method under Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Cefotiam Hydrochloride RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

3. Determine the \(^1{}\text{H}\) spectrum of a solution of Cefotiam Hydrochloride in heavy water for nuclear magnetic resonance spectroscopy (1 in 10) as directed under Nuclear Magnetic Resonance Spectroscopy, using sodium 3-trimethylsilylpropanesulfonate for sodium magnetic resonance spectroscopy as an internal reference compound: it exhibits single signals at around \(\delta 3.1\) ppm and at around \(\delta 6.7\) ppm, respectively. The ratio of integrated intensity of each signal is about 6:1.

4. Dissolve 0.1 g of Cefotiam Hydrochloride in 5 mL of dilute nitric acid, and immediately add 1 mL of silver nitrate TS: a white precipitate is formed.

**Optical rotation** \(\angle 2.49\) \([\theta]_D^{20} +60 - +72^\circ\) (1 g calculated on the anhydrous bases, water, 100 mL, 100 mm).

**pH** \(\angle 2.54\) Dissolve 1.0 g of Cefotiam Hydrochloride in 10 mL of water: the pH of the solution is between 1.2 and 1.7.

**Purity**

1. Clarity of solution—Dissolve 1.0 g of Cefotiam Hydrochloride in 10 mL of water: the solution is clear, and colorless to yellow.

2. Heavy metals \(\angle 1.07\) —To 1.0 g of Cefotiam Hydrochloride add 1 mL of sulfuric acid, and heat gently to carbonize. After cooling, add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), fire the ethanol to burn, then heat gradually to incinerate. If a carbonized residue still retains, moisten the residue with a little amount of sulfuric acid, and ignite again to incinerate. After cooling, add 2 mL of hydrochloric acid to the residue, heat on a water bath to dissolve, then heat to dryness. Add 10 mL of water, and heat to dissolve. After cooling, add ammonia TS dropwise to adjust to pH 3 – 4, if necessary, filter, wash the residue on the filter with 10 mL of water, transfer the filtrate and washings into a Nessler tube, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 2.0 mL of Standard Lead Solution in the same manner as for preparation of the test solution (not more than 20 ppm).

3. Arsenic \(\angle 1.11\) —Incinerate 1.0 g of Cefotiam Hydrochloride according to Method 4. After cooling, add 10 mL of dilute hydrochloric acid to the residue, heat to dissolve on the water bath, and use this solution as the test solution. Perform the test (not more than 2 ppm).

**Water** \(\angle 2.48\) Not more than 7.0% (0.25 g, volumetric titration, direct titration. Use 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 Cefotiam Hydrochloride and Cefotiam Hydrochloride RS, equivalent to about 0.1 g (potency), and dissolve each in the mobile phase to make exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 10 \(\mu L\) each of the sample solution and standard solution as directed under Liquid Chromatography, according to the following conditions, and determine the peak areas, \(A_1\) and \(A_2\), of cefotiam of these solutions.

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\text{Amount} [\mu g \text{ (potency)}] \text{ of cefotiam } (\text{C}_{18}\text{H}_{23}\text{N}_{9}\text{O}_{4}\text{S}_{3}) = M_5 \times A_1/A_2 \times 1000
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M_5: \text{Amount} [\text{mg (potency)}] \text{ of Cefotiam Hydrochloride RS}
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**Operating conditions**

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

Column: A stainless steel column 4.0 mm in inside diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 \(\mu m\) in particle diameter).

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

Mobile phase: To 800 mL of 0.05 mol/L disodium hydrogenphosphate TS add 0.05 mol/L potassium dihydrogenphosphate TS to adjust the pH to 7.7. To 440 mL of this solution add 60 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefotiam is about 14 minutes.

**System suitability**

System performance: Dissolve 0.04 g of orcein in 10 mL of...
Cefotiam Hydrochloride for Injection

Cefotiam Hydrochloride for Injection is a preparation for injection which is dissolved before use. It contains not less than 90.0% and not more than 110.0% of the labeled amount of cefotiam (C₁₈H₂₃N₉O₄S₃: 525.63).

**Method of Preparation** Prepare as directed under Injection, with Cefotiam Hydrochloride.

**Description** Cefotiam Hydrochloride for Injection occurs as a white to light yellow powder.

**Identification (1)** Determine the absorption spectrum of a solution of Cefotiam Hydrochloride for Injection (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 257 nm and 261 nm.

**Identification (2)** Dissolve 50 mg of Cefotiam Hydrochloride for Injection in 0.5 mL of heavy water for nuclear magnetic resonance spectroscopy, and determine the spectrum of this solution as directed under Nuclear Magnetic Resonance Spectroscopy <2.24> (H), using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits a single signal A between δ 2.7 ppm and δ 3.0 ppm, and a single signal B at around δ 6.5 ppm. The ratio of the integrated intensity of each signal, A:B, is about 6:1.

**pH** <2.54> The pH of a solution prepared by dissolving an amount of Cefotiam Hydrochloride for Injection, equivalent to 0.5 g (potency) according to the labeled amount, in 5 mL of water is between 5.7 and 7.2.

**Purity** Clarity and color of solution—Dissolve an amount of Cefotiam Hydrochloride for Injection, equivalent to 1.0 g (potency) of Cefotiam Hydrochloride according to the labeled potency, in 10 mL of water: the solution is clear, and the absorbance of this solution, determined at 450 nm 10 minutes after dissolving as directed under Ultraviolet-visible Spectrophotometry <2.24>, is not more than 0.20.

**Loss on drying** <2.41> Not more than 6.0% (0.5 g, in vacuum, 60°C, 3 hours).

**Bacterial endotoxins** <4.01> Less than 0.125 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> Perform the test according to Method 1: it meets the requirement.

**Sterility** <4.06> Perform the test according to the Membrane filtration method: it meets the requirement.

**Assay** Weigh accurately the contents of not less than 10 Cefotiam Hydrochloride for Injection. Weigh accurately an amount of the content, equivalent to about 50 mg (potency) of Cefotiam Hydrochloride according to the labeled amount, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg (potency) of Cefotiam Hydrochloride RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Proceed as directed in the Assay under Cefotiam Hydrochloride.

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M_S = M_A \times A_S \times 1000
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\(M_A\): Amount [mg (potency)] of cefotiam (C₁₈H₂₃N₉O₄S₃)

\(M_S\): Amount [mg (potency)] of Cefotiam Hydrochloride RS

**Operating conditions**—Proceed as directed in the Assay under Cefotiam Hydrochloride.

**System Suitability**—Proceed as directed in the Assay under Cefotiam Hydrochloride.

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

Cefozopran Hydrochloride

Cefozopran Hydrochloride contains not less than 860 μg (potency) and not more than 960 μg (potency) per mg, calculated on the anhydrous basis. The potency of Cefozopran Hydrochloride is expressed as mass (potency) of cefozopran (C₁₉H₁₇N₉O₅S₂.HCl: 551.99) per mg.

**Description** Cefozopran Hydrochloride occurs as a white to pale yellow, crystals or crystalline powder. It is freely soluble in dimethylsulfoxide and in formamide, slightly soluble in water, in methanol and in ethanol (95), and practically insoluble in acetonitrile and diethyl ether.