CEFTRIAXONE SODIUM  
(CEFTRIAXONUM NATRICUM)  

Draft for The International Pharmacopoeia  
(July 2016)  

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr Herbert Schmidt, Medicines Quality Assurance, Technologies Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidt@who.int; fax: (+41 22) 791 4730 by 16 September 2016.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/15.644
Draft for *The International Pharmacopoeia*
Ceftriaxone sodium
(Ceftriaxonum natricum)

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CEFTRIAXONE SODIUM
(CEFTRIAXONUM NATRICUM)

C_{18}H_{16}N_{8}Na_{2}O_{7}S_{3},3\frac{1}{2}H_{2}O

Relative molecular mass. 661.60


Description. Almost white or yellowish, slightly hygroscopic, crystalline powder.

Solubility. Freely soluble in water, sparingly soluble in methanol, very slightly soluble in anhydrous ethanol.

Labelling. The label states, where applicable:

- that the substance is free of bacterial endotoxins;
- that the substance is sterile.

Category. Antibacterial

Storage. Ceftriaxone sodium should be kept in an air-tight container protected from light. If the substance is sterile, store in a sterile and air-tight container protected from light.

Manufacture. Where necessary, the production method is validated to demonstrate that the substance, if tested, would comply with limits of not more than 20 ppm for N,N-dimethylaniline and 0.8% for 2-ethylhexanoic acid.

Additional information. Ceftriaxone sodium is a semi-synthetic product derived from a fermentation product.
Requirements

Ceftriaxone sodium contains not less than 96.0% and not more than 102.0% of \( \text{C}_{18}\text{H}_{16}\text{N}_{8}\text{Na}_{2}\text{O}_{2}\text{S}_{3} \), calculated with reference to the anhydrous substance.

Identity tests

- Either tests A and C or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from ceftriaxone sodium RS or with the reference spectrum of ceftriaxone sodium.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under the Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak corresponding to ceftriaxone in the chromatogram obtained with solution (2).

C. When tested for sodium as described under 2.1 General identification tests, yields the characteristic reaction.

Specific optical rotation (1.4). Dissolve 0.250 g in water \( \text{R} \) and dilute to 25.0 mL with the same solvent. Calculate with reference to the anhydrous substance; \([\alpha]_{D}^{20^\circ} = -155^\circ \) to \(-170^\circ\).

Clarity and colour of solution. Dissolve 2.40 g in carbon-dioxide-free water \( \text{R} \) and dilute to 20.0 mL with the same solvent (Solution A). Dilute 2 mL of Solution A to 20 mL carbon-dioxide-free water \( \text{R} \). The solution is clear and not more intensely coloured than reference solution \( Y_5 \) or \( BY_5 \) when compared as described under 1.11.2 Degree of colouration of liquids. (Keep the remaining solution (Solution A) for the “pH value”.)

Note from the Secretariat. The chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of colouration of liquids.

pH value (1.13). pH of the solution prepared for the “Clarity and colour of solution” (Solution A), 6.0 to 8.0.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 0.100 g of the test substance. The water content is not less than 80 mg per g and not more than 110 mg per g.

Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out...
Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under assay method.

Prepare the following solutions in mobile phase: for solution (1) dissolve about 30 mg of the test substance and dilute to 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity A to 100.0 mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0. Ceftriaxone impurity A is eluted at a relative retention of about 1.4 with reference to ceftriaxone (retention time about 9 min).

Inject alternately 20 µL each of solution (1) and (2). Record the chromatograms for about 2 times the retention time of ceftriaxone.

In the chromatogram obtained with solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

As the mobile phase use a solution prepared as follows: dissolve 2.0 g of tetradecylammonium bromide R and 2.0 g of tetraheptylammonium bromide R in a

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1 Hypersil BDS C18 has been found suitable.
mixture of 440 mL of water, 55 mL of phosphate buffer pH 7.0 (0.067 mol/L) TS, 5.0 mL of citrate buffer pH 5.0 TS and 500 mL of acetonitrile R and filter.

Prepare the following solutions in mobile phase. For solution (1) dissolve 30 mg of the test substance, accurately weighed and dilute to 100.0 mL. For solution (2) dissolve about 30 mg of ceftriaxone sodium RS, accurately weighed and dilute to 100.0 mL. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and about 5 mg of ceftriaxone impurity A and dilute to 100.0 mL.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0.

Inject alternately 20 µL each of solution (1) and (2). Measure the areas of the peaks corresponding to ceftriaxone and calculate the percentage content of C₁₈H₁₆N₈Na₂O₇S₃, using the declared content of C₁₈H₁₆N₈Na₂O₇S₃ in ceftriaxone sodium RS.

**Sterility.** If intended for use in the manufacture of a parenteral dosage form without a further appropriate sterilization procedure, complies with 3.2 Test for sterility.

**Impurities**

[Note from the Secretariat. The structures of the impurities will be added at a later stage.]

A. (6R,7R)-7-[(E)-2-[(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Ceftriaxone E-isomer).

B. (Z)-2-[(2-Aminothiazol-4-yl)-N-[(5aR,6R)-1,7-dioxo-1,3,4,5a,6,7-hexahydroazeto[2,1-b]furo[3,4-d][1,3]thiazin-6-yl]-2-(methoxyimino)acetamido. (Deacetylcefotaxime lactone).

C. (6R,7R)-7-Amino-3-[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Deacetylceftriaxone).

D. (Z)-S-Benzothiazol-2-yl 2-[(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate (Ceftriaxone benzothiazolyl oxime).


F. 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione. (Ceftriaxone triazine analog)
G. \((6R,7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-\{[(6-
hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl\}-8-oxo-5-thia-1-
azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid \(\text{(Ceftriaxone 3-ene isomer)}\).

**Reagent to be included:**

**Citrate buffer, pH 5 TS**

*Procedure.* Dissolve 20.17 g of citric acid R in 800 ml of water R, adjust to pH 5.0 with
sodium hydroxide (~400 g/L) TS and dilute to 1000 mL with water R.

**Tetradecylammonium bromide R**

C\(_{40}\)H\(_{84}\)BrN. Chromatographic reagent grade of commerce.

*Description.* White to almost white crystals, or a crystalline powder.

*Melting point.* 88-89 °C

**Tetraheptylammonium bromide R**

C\(_{28}\)H\(_{60}\)BrN. Chromatographic reagent grade of commerce.

*Description.* White, flaky powder.

*Melting range.* Between 89-91°C.

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