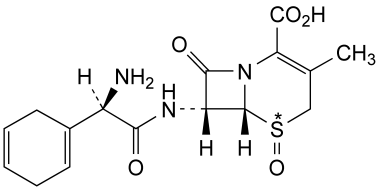
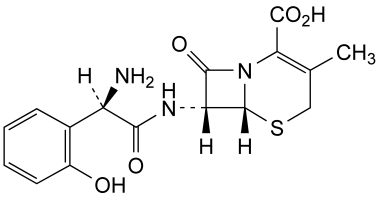
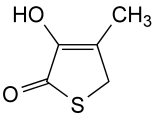


C. (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5-oxide (isomer 1),

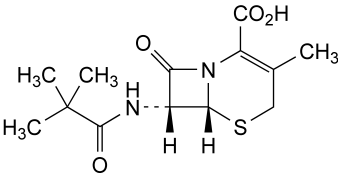
D. (6*R*,7*R*)-7-[[(2*R*)-amino(cyclohexa-1,4-dienyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 5-oxide (isomer 2),



E. ((6*R*,7*R*)-7-[[(2*R*)-amino(2-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



F. 3-hydroxy-4-methylthiophen-2(5*H*)-one,

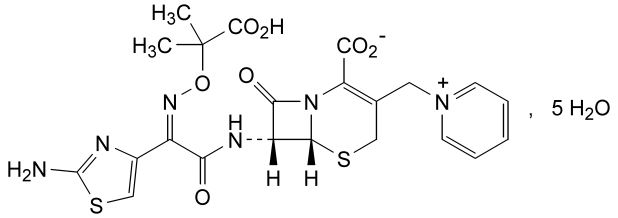


G. (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ADCA pivalamide).

01/2008:1405

CEFTAZIDIME

Ceftazidimum



$C_{22}H_{22}N_6O_7S_2,5H_2O$ M_r 637

[78439-06-2]

DEFINITION

Ceftazidime is (6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate. It contains not less than 95.0 per cent and not more than 102.0 per cent of $C_{22}H_{22}N_6O_7S_2$, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, slightly soluble in water and in methanol, practically insoluble in acetone and in alcohol. It dissolves in acid and alkali solutions.

IDENTIFICATION

Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *ceftazidime CRS*.

TESTS

Solution S. Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 50 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 3.0 to 4.0.

Related substances

A. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel F_{254} plate R*.

Test solution. Dissolve 0.100 g of the substance to be examined in a 36 g/l solution of *disodium hydrogen phosphate R* and dilute to 2.0 ml with the same solution.

Reference solution. Dilute 1 ml of the test solution to 200 ml with a 36 g/l solution of *disodium hydrogen phosphate R*.

Apply to the plate 2 µl of each solution. Develop over a path of 15 cm using a mixture of 6 volumes of *butanol R*, 26 volumes of *sodium acetate buffer solution pH 4.5 R*, 32 volumes of *butyl acetate R* and 32 volumes of *glacial acetic acid R*. Dry the plate in a current of warm air and examine in ultraviolet light at 254 nm. Any spot with an R_F value greater than that of the principal spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

B. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 20.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 20.0 ml with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *ceftazidime impurity A CRS* in the mobile phase and dilute to 20.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 20.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *ceftazidime impurity A CRS* and 5 mg of *ceftazidime CRS* in the mobile phase and dilute to 20.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 20.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1.3 ml/min a mixture of 7 volumes of *acetonitrile R* and 93 volumes of a 22.6 g/l solution of *ammonium dihydrogen phosphate R*, adjusted to pH 3.9 with a 10 per cent *V/V* solution of *phosphoric acid R*,

– as detector a spectrophotometer set at 255 nm,

maintaining the temperature of the column at 35 °C.

Inject 20 µl of reference solution (b). Adjust the sensitivity of the system so that the heights of the 2 peaks in the chromatogram obtained are at least 50 per cent of the full scale of the recorder. The test is not valid unless in

the chromatogram obtained, the resolution between the peaks corresponding to ceftazidime and impurity A is at least 5.9. Inject 20 µl of the test solution and 20 µl of reference solution (a). Continue the chromatography of the test solution for 3 times the retention time of ceftazidime. In the chromatogram obtained with the test solution: the area of any peak, apart from the principal peak, is not greater than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2 per cent). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a).

Impurity F. Not more than 500 ppm, determined by liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.500 g of the substance to be examined in a 10 per cent *V/V* solution of *phosphate buffer solution pH 7.0 R4* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve 1.00 g of *pyridine R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of the solution to 200.0 ml with *water R*. To 1.0 ml of the solution, add 10 ml of *phosphate buffer solution pH 7.0 R4* and dilute to 100.0 ml with *water R*.

Reference solution (b). Dilute 1.0 ml of the test solution to 200.0 ml with a 10 per cent *V/V* solution of *phosphate buffer solution pH 7.0 R4*. To 1.0 ml of the solution add 20 ml of reference solution (a) and dilute to 200 ml with a 10 per cent *V/V* solution of *phosphate buffer solution pH 7.0 R4*.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.25 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1.0 ml/min a mixture of 8 volumes of a 28.8 g/l solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 7.0 with *ammonia R*, 24 volumes of *acetonitrile R* and 68 volumes of *water R*,

– as detector a spectrophotometer set at 255 nm,

Inject 20 µl of reference solution (b). The test is not valid unless in the chromatogram obtained, the resolution between the peaks due to ceftazidime and to impurity F is at least 7.0.

Inject 20 µl of reference solution (a). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained is at least 50 per cent of the full scale of the recorder. Inject reference solution (a) 6 times. The test is not valid unless the relative standard deviation of the area of the principal peak is at most 1.0 per cent. Inject alternately 20 µl of the test solution and 20 µl of reference solution (a).

Water (*2.5.12*): 13.0 per cent to 15.0 per cent, determined on 0.200 g by the semi-micro determination of water.

Bacterial endotoxins (*2.6.14*): less than 0.10 IU/mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dissolve 25.0 mg of *ceftazidime CRS* in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (b). Dissolve 5 mg of *ceftazidime impurity A CRS* in 5.0 ml of reference solution (a).

The chromatographic procedure may be carried out using:

– a column 0.15 m long and 4.6 mm in internal diameter packed with *hexylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 2 ml/min a mixture prepared as follows: dissolve 4.26 g of *disodium hydrogen phosphate R* and 2.73 g of *potassium dihydrogen phosphate R* in 980 ml of *water R*, then add 20 ml of *acetonitrile R*,

– as detector a spectrophotometer set at 245 nm.

Inject 20 µl of reference solution (b). Adjust the sensitivity of the system so that the heights of the 2 principal peaks in the chromatogram obtained are at least 50 per cent of the full scale of the recorder. The test is not valid unless, in the chromatogram obtained, the resolution between the peaks corresponding to ceftazidime and impurity A is at least 1.0. Inject alternately the test solution and reference solution (a). Calculate the percentage content of ceftazidime.

STORAGE

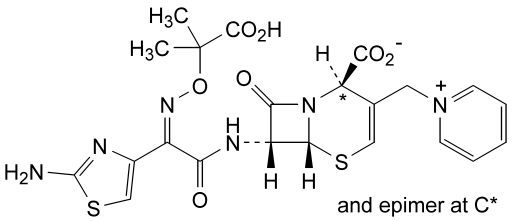
Store in an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

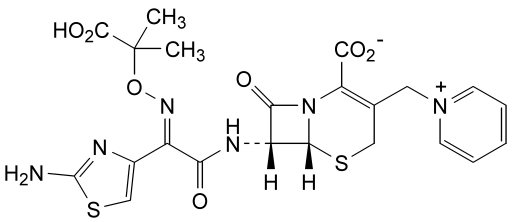
By liquid chromatography (related substances test): A, B, C.

By thin-layer chromatography (related substances test): D, E.

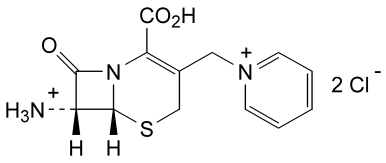
By liquid chromatography (impurity F test): F.



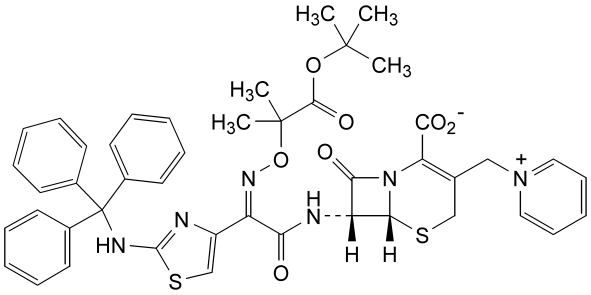
A. (2*RS*,6*R*,7*R*)-7-[[(*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ-2-ceftazidime),



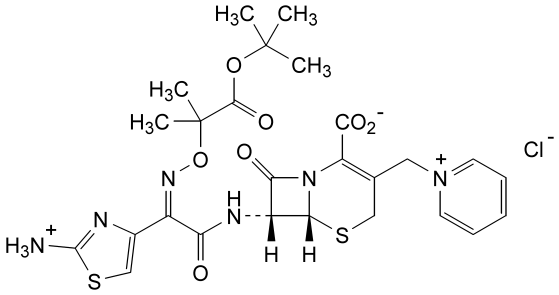
B. (6*R*,7*R*)-7-[[(*E*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



C. (6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-aminium dichloride,



D. (6*R*,7*R*)-7-[[(*Z*)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]-2-[2-[(triphenylmethyl)amino]thiazol-4-yl]acetyl]amino]-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



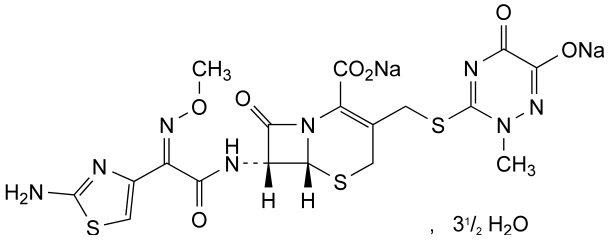
E. (6*R*,7*R*)-7-[[(*Z*)-2-(2-ammoniothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate chloride,

F. pyridine.

01/2008:0991

CEFTRIAXONE SODIUM

Ceftriaxonum natricum



$C_{18}H_{16}N_8Na_2O_7S_3,3^1/_2H_2O$ M_r 662

[104376-79-6]

DEFINITION

Disodium (6*R*,7*R*)-7-[[(*2Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5 hydrate.

Semi-synthetic product derived from a fermentation product.

Content: 96.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: almost white or yellowish, slightly hygroscopic, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *ceftriaxone sodium CRS*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.40 g in *carbon dioxide-free water R* and dilute to 20.0 ml with the same solvent.

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 or BY_5 (*2.2.2*).

Dilute 2 ml of solution S to 20 ml with *water R*.

pH (*2.2.3*): 6.0 to 8.0 for solution S.

Specific optical rotation (*2.2.7*): – 155 to – 170 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 30.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 30.0 mg of *ceftriaxone sodium CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *ceftriaxone sodium CRS* and 5.0 mg of *ceftriaxone impurity A CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 2.0 g of *tetradecylammonium bromide R* and 2.0 g of *tetraheptylammonium bromide R* in a mixture of 440 ml of *water R*, 55 ml of *0.067 M phosphate buffer solution pH 7.0 R*, 5.0 ml of citrate buffer solution pH 5.0 prepared by dissolving 20.17 g of *citric acid R* in 800 ml of *water R*, adjusting to pH 5.0 with *strong sodium hydroxide solution R* and diluting to 1000.0 ml with *water R*, and 500 ml of *acetonitrile R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µl of the test solution and reference solutions (b) and (c).

Run time: twice the retention time of ceftriaxone.

System suitability: reference solution (b):

– *resolution*: minimum 3.0 between the peaks due to ceftriaxone and impurity A.

Limits:

– *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);