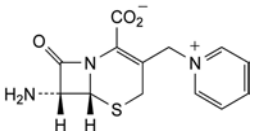
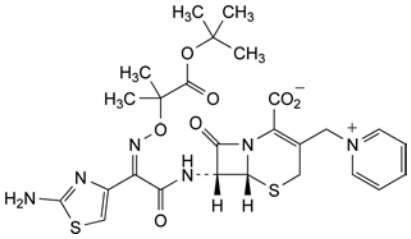
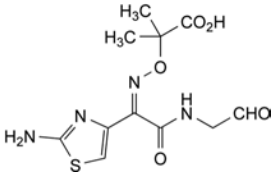


C. (6*R*,7*R*)-7-amino-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

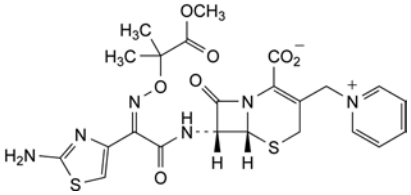


E. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

F. pyridine,



G. 2-[[[(1*Z*)-1-(2-aminothiazol-4-yl)-2-[(oxoethyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic acid,



H. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

07/2009:2344

CEFTAZIDIME PENTAHYDRATE WITH SODIUM CARBONATE FOR INJECTION

Ceftazidimum pentahydricum et natrii carbonas ad iniectabile

DEFINITION

Sterile mixture of *Ceftazidime pentahydrate (1405)* and *Anhydrous sodium carbonate (0773)*.

Ceftazidime pentahydrate is a semi-synthetic product derived from a fermentation product.

Content:

– *ceftazidime*: 93.0 per cent to 105.0 per cent (dried and carbonate-free substance);

– *sodium carbonate*: 8.0 per cent to 10.0 per cent.

CHARACTERS

Appearance: white or pale yellow powder.

Solubility: freely soluble in water and in methanol, practically insoluble in acetone.

IDENTIFICATION

A. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (a).

B. It gives the reaction of carbonates (*2.3.1*).

TESTS

Solution S. Dissolve 2.60 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 425 nm is not greater than 0.50.

pH (*2.2.3*): 5.0 to 7.5 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Suspend 0.150 g of the substance to be examined in 5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 100 mL with the same solvent.

Reference solution (a). To 1.0 mL of the test solution add 5.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 5.0 mL with *water R*.

Reference solution (b). Suspend 3 mg of *ceftazidime CRS* and 3 mg of *ceftazidime impurity A CRS* in 5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 20 mL with the same solvent. Dilute 1 mL of this solution to 20 mL with *water R*.

Reference solution (c). Suspend 3 mg of *ceftazidime for peak identification CRS* (containing impurities A, B and G) in 0.5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 2 mL with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: solution containing 3.6 g of *disodium hydrogen phosphate R* and 1.4 g of *potassium dihydrogen phosphate R* in 1 litre of *water R*, adjusted to pH 3.4 with a 10 per cent *V/V* solution of *phosphoric acid R*;

– *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	96 → 89	4 → 11
4 - 5	89	11
5 - 8	89 → 84	11 → 16
8 - 11	84 → 80	16 → 20
11 - 15	80 → 50	20 → 50
15 - 18	50 → 20	50 → 80
18 - 22	20	80

Flow rate: 1.3 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Relative retention with reference to ceftazidime (retention time = about 8 min): impurity F = about 0.4; impurity G = about 0.8; impurity A = about 0.9; impurity B = about 1.4.

Identification of impurities: use the chromatogram supplied with *ceftazidime for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and G.

System suitability: reference solution (b):

– *resolution*: minimum 4.0 between the peaks due to impurity A and ceftazidime.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity G by 3.0;

– *impurities A, B, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to impurity F.

Impurity F. 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 phosphate buffer solution pH 7.0 R4* and dilute to 100.0 mL with the same buffer solution.

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 this solution to 200.0 mL with *water R*. To 1.0 mL of this solution add 10.0 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 phosphate buffer solution pH 7.0 R4*. To 1.0 mL of this solution add 20.0 mL of reference solution (a) and dilute to 200.0 mL with a 10 per cent *V/V phosphate buffer solution pH 7.0 R4*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 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*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 255 nm.

Injection: 20 µL.

Run time: 10 min.

System suitability: reference solution (b):

– *resolution*: minimum 7.0 between the peaks due to ceftazidime and impurity F.

Limit:

– *impurity F*: not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Loss on drying (*2.2.32*): maximum 13.5 per cent, determined on 0.300 g. Dry *in vacuo* at 25 °C at a pressure not exceeding 0.67 kPa for 4 h then heat the residue *in vacuo* at 100 °C at a pressure not exceeding 0.67 kPa for 3 h.

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

ASSAY

Ceftazidime. 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 5.0 mg of *ceftazidime impurity A CRS* in 5.0 mL of reference solution (a).

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

– *stationary phase*: *hexylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 4.3 g of *disodium hydrogen phosphate R* and 2.7 g of *potassium dihydrogen phosphate R* in 980 mL of *water R*, then add 20 mL of *acetonitrile R*.

Flow rate: 2 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 20 µL.

Run time: 6 min.

Relative retention with reference to ceftazidime (retention time = about 4.5 min): impurity A = about 0.7.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurity A and ceftazidime.

Calculate the content of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) from the declared content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime CRS*.

Sodium carbonate. Atomic absorption spectrometry (*2.2.23, Method I*).

Caesium chloride buffer solution. To 12.7 g of *caesium chloride R* add 500 mL of *water R* and 86 mL of *hydrochloric acid R* and dilute to 1000.0 mL with *water R*.

Sodium standard solution (1000 mg/L). Dissolve 3.70 g of *sodium nitrate R* in *water R* and dilute to 500 mL with the same solvent, add 48.5 g of *nitric acid R* and dilute to 1000 mL with *water R*.

Test solution. Dissolve 650.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent. To 10.0 mL of this solution add 5.0 mL of caesium chloride buffer solution and dilute to 50.0 mL with *water R*.

Reference solution. Into 4 identical flasks, each containing 20.0 mL of caesium chloride buffer solution, introduce respectively 0 mL, 5.00 mL, 10.00 mL and 15.00 mL of sodium standard solution (1000 mg/L) and dilute to 200.0 mL with *water R*.

Source: sodium hollow-cathode lamp.

Wavelength: 330.2 nm to 330.3 nm.

Atomisation device: air-acetylene flame.

Calculate the percentage content of sodium carbonate.

STORAGE

In a sterile, airtight, tamper-proof container, protected from light and humidity.

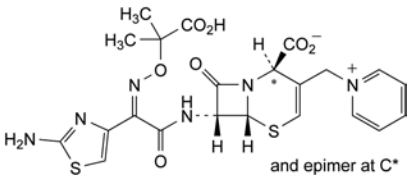
LABELLING

The label states the percentage content *m/m* of ceftazidime.

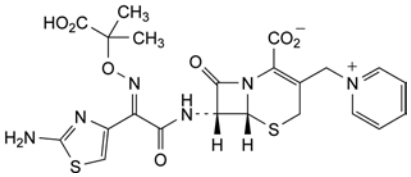
IMPURITIES

Specified impurities: A, B, F, G.

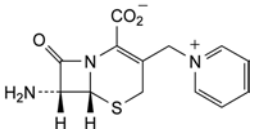
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *C, E, H.*



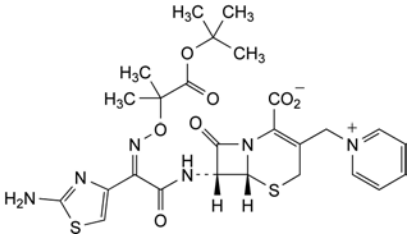
A. (2*RS*,6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ-2-ceftazidime),



B. (6*R*,7*R*)-7-[[(2*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,

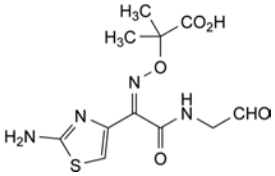


C. (6*R*,7*R*)-7-amino-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

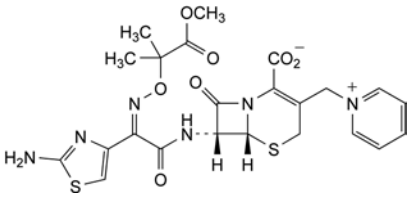


E. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]-amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

F. pyridine,



G. 2-[[[(1*Z*)-1-(2-aminothiazol-4-yl)-2-[(oxoethyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic acid,

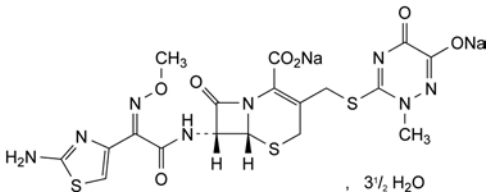


H. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

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)sulfanyl]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