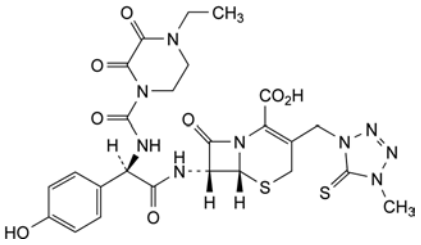
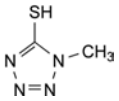
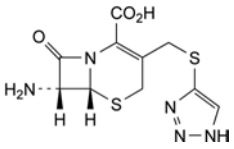


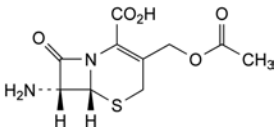
B. (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]-amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[(4-methyl-5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



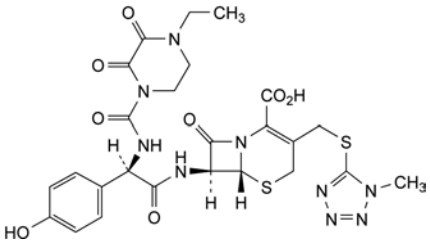
C. 1-methyl-1*H*-tetrazole-5-thiol,



D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*H*-1,2,3-triazol-4-yl-sulfanyl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-TACA),



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

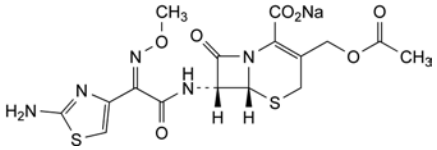


F. (6*R*,7*S*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazine-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

01/2008:0989

CEFOTAXIME SODIUM

Cefotaximum natricum



$C_{16}H_{16}N_5NaO_7S_2$ M_r 477.4
[64485-93-4]

DEFINITION

Sodium (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

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

CHARACTERS

Appearance: white or slightly yellow powder, hygroscopic.

Solubility: freely soluble in water, sparingly soluble in methanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *cefotaxime sodium CRS*.

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

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*). Add 1 mL of *glacial acetic acid R* to 10 mL of solution S. The solution, examined immediately, is clear.

pH (*2.2.3*): 4.5 to 6.5 for solution S.

Specific optical rotation (*2.2.7*): + 58.0 to + 64.0 (anhydrous substance).

Dissolve 0.100 g in *water R* and dilute to 10.0 mL with the same solvent.

Absorbance (*2.2.25*): maximum 0.40 at 430 nm for solution S.

Specific absorbance (*2.2.25*): 360 to 390, determined at the absorption maximum at 235 nm (anhydrous substance).

Dissolve 20.0 mg in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A: mobile phase B, mobile phase A (14:86 *V/V*).

Test solution. Dissolve 40.0 mg of the substance to be examined in solution A and dilute to 50.0 mL with the same solution.

Reference solution (a). Dissolve 8.0 mg of *cefotaxime acid CRS* in solution A and dilute to 10.0 mL with the same solution.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with solution A.

Reference solution (c). Add 1.0 mL of *dilute hydrochloric acid R* to 4.0 mL of the test solution. Heat the solution at 40 °C for 2 h. Add 5.0 mL of *buffer solution pH 6.6 R* and 1.0 mL of *dilute sodium hydroxide solution R*.

Reference solution (d). Dissolve 4 mg of *cefotaxime for peak identification CRS* (containing impurities A, B, C, E and F) in 5 mL of solution A.

Column:
- *size*: *l* = 0.15 m, Ø = 3.9 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 30 °C.

Mobile phase:
- *mobile phase A*: 7.1 g/L solution of *disodium hydrogen phosphate R* adjusted to pH 6.25 using *phosphoric acid R*;
- *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	86	14
7 - 9	86 → 82	14 → 18
9 - 16	82	18
16 - 45	82 → 60	18 → 40
45 - 50	60	40
50 - 55	60 → 86	40 → 14
55 - 60	86	14

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities: use the chromatogram supplied with *cefotaxime for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, E and F.

Relative retention with reference to cefotaxime (retention time = about 13 min): impurity B = about 0.3; impurity A = about 0.5; impurity E = about 0.6; impurity C = about 1.9; impurity D = about 2.3; impurity F = about 2.4; impurity G = about 3.1.

System suitability: reference solution (c):

– *resolution*: minimum 3.5 between the peaks due to impurity E and cefotaxime;

– *symmetry factor*: maximum 2.0 for the peak due to cefotaxime.

Limits:

– *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

– *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent);

– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Ethanol (*2.4.24, System A*): maximum 1.0 per cent.

***N,N*-Dimethylaniline** (*2.4.26, Method B*): maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*): maximum 0.5 per cent *m/m*.

Water (*2.5.12*): maximum 3.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*): less than 0.05 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (a).

Calculate the percentage content of $C_{16}H_{16}N_5NaO_7S_2$ by multiplying the percentage content of cefotaxime by 1.048.

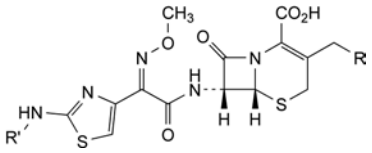
STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

Specified impurities: A, B, C, D, E, F.

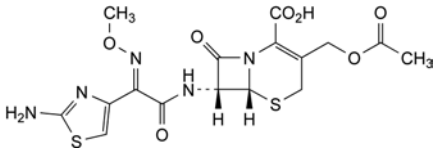
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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): G.*



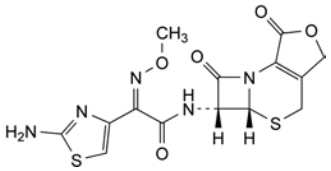
A. R = R′ = H: (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetoxycefotaxime),

B. R = OH, R′ = H: (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (deacetylcefotaxime),

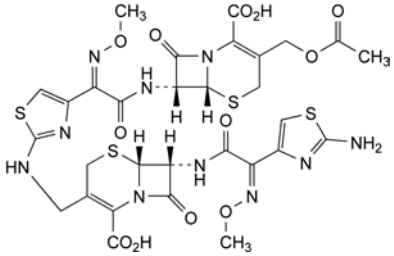
C. R = O-CO-CH_3, R′ = CHO: (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-(formylamino)thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*N*-formylcefotaxime),



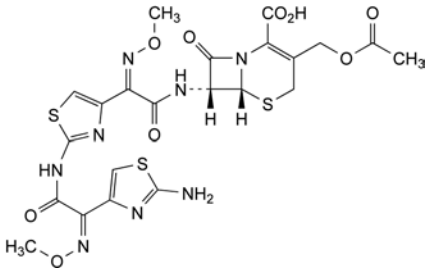
D. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*E*-cefotaxime),



E. (5a*R*,6*R*)-6-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (deacetylcefotaxime lactone),



F. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-[[[(6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-yl]methyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefotaxime dimer),

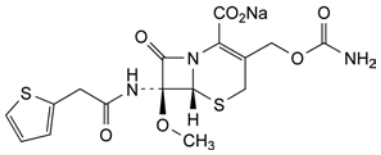


G. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(2*Z*)-2-[2-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetyl]amino]thiazol-4-yl]-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (ATA cefotaxime).

01/2008:0990
corrected 6.0

CEFOXITIN SODIUM

Cefoxitinum natricum



$C_{16}H_{16}N_3NaO_7S_2$ M_r 449.4
[33564-30-6]

DEFINITION

Sodium (6*R*,7*S*)-3-[(carbamoyloxy)methyl]-7-methoxy-8-oxo-7-[[(thiophen-2-yl)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

Semi-synthetic product derived from a fermentation product.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder, very hygroscopic.

Solubility: very soluble in water, sparingly soluble in alcohol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *cefoxitin sodium CRS*.

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

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*): 4.2 to 7.0.

Dilute 2 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Specific optical rotation (*2.2.7*): + 206 to + 214 (anhydrous substance).

Dissolve 0.250 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Absorbance (*2.2.25*). Dissolve 0.100 g in *water R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *sodium hydrogen carbonate solution R*. Examined between 220 nm and 350 nm, the solution shows an absorption maximum at 236 nm and a broad absorption maximum at about 262 nm. The specific absorbance at this broad maximum is 190 to 210 (anhydrous substance).

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solution A. Dilute 20 mL of a 34.8 g/L solution of *dipotassium hydrogen phosphate R* adjusted to pH 6.8 with *phosphoric acid R* to 1000 mL with *water R*.

Test solution. Dissolve 50.0 mg of the substance to be examined in solution A and dilute to 10.0 mL with the same solution.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with solution A.

Reference solution (b). To 1.0 mL of the test solution add 7.0 mL of *water R* and 2.0 mL of *methanol R*. Add 25 mg of *sodium carbonate R*, stir for 10 min at room temperature, then heat in a water-bath at 70 °C for 30 min. Allow to cool. Add 3 drops of *glacial acetic acid R* and 1 mL of the test solution and mix.

Column:
– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *phenylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 300 m^2/g and a pore size of 7 nm.

Mobile phase:
– *mobile phase A*: *water R* adjusted to pH 2.7 with *anhydrous formic acid R*,
– *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	90	10
12 - 37	90 → 80	10 → 20
37 - 50	80 → 60	20 → 40
50 - 55	60 → 20	40 → 80
55 - 60	20	80
60 - 62	20 → 90	80 → 10
62 - 70	90	10

Flow rate: 1 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 50 µL.

Relative retentions with reference to cefoxitin (retention time = about 34 min): impurity A = about 0.82; impurity B = about 1.16; impurity C = about 1.27; impurity D = about 1.31.

System suitability: reference solution (b):
– *resolution*: minimum 5.0 between the 2 principal peaks.

Limits:
– *any impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (4.0 per cent),
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 1.0 per cent, determined on 0.500 g.

Bacterial endotoxins (*2.6.14*): less than 0.13 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (a). Dissolve 25.0 mg of *cefoxitin sodium CRS* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (b). Dissolve 20.0 mg of *2-(2-thienyl)acetic acid R* in *water R* and dilute to 25.0 mL with the same solvent.

Reference solution (c). Mix 1.0 mL of reference solution (a) and 5.0 mL of reference solution (b).

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

Mobile phase: *acetic acid R, acetonitrile R, water R* (1:19:81 *V/V/V*).

Flow rate: 1 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL; inject the test solution and reference solutions (a) and (c).