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);

– *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (c) (4.0 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

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

2-Ethylhexanoic acid (*2.4.28*): maximum 0.8 per cent *m/m*.

Water (*2.5.12*): 8.0 per cent to 11.0 per cent, determined on 0.100 g.

Bacterial endotoxins (*2.6.14*): less than 0.08 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.

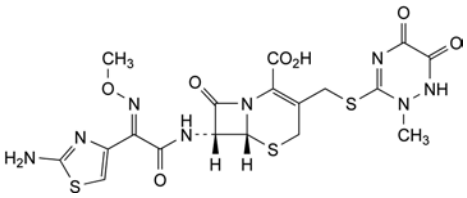
Injection: test solution and reference solution (a).

Calculate the percentage content of $C_{18}H_{16}N_8Na_2O_7S_3$ from the declared content of *ceftriaxone sodium CRS*.

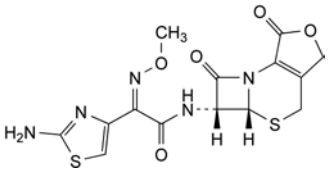
STORAGE

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

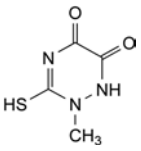
IMPURITIES



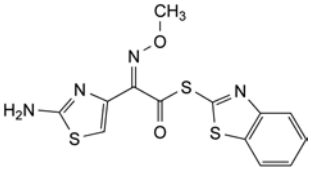
A. (6*R*,7*R*)-7-[[(2*E*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (*(E)*-isomer),



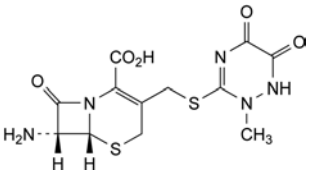
B. (5a*R*,6*R*)-6-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



C. 2-methyl-3-sulfanyl-1,2-dihydro-1,2,4-triazine-5,6-dione,



D. *S*-benzothiazol-2-yl (2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)thioacetate,

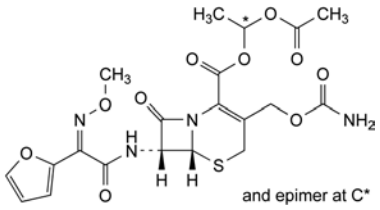


E. (6*R*,7*R*)-7-amino-3-[[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

01/2008:1300
corrected 6.0

CEFUROXIME AXETIL

Cefuroximum axetili



$C_{20}H_{22}N_4O_{10}S$ M_r 510.5
[64544-07-6]

DEFINITION

Mixture of the 2 diastereoisomers of (1*RS*)-1-(acetyloxy)ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-2-(furan-2-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 almost white powder.

Solubility: slightly soluble in water, soluble in acetone, in ethyl acetate and in methanol, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefuroxime axetil CRS*.

B. Examine the chromatograms obtained in the assay.

Results: the principal peaks in the chromatogram obtained with the test solution are similar in retention time and size to the peaks due to cefuroxime axetil diastereoisomers A and B in the chromatogram obtained with reference solution (d).

TESTS

Related substances. Liquid chromatography (*2.2.29*): use the normalisation procedure. *Prepare the test solution and reference solution (d) immediately before use.*

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

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

Reference solution (b). In order to prepare *in situ* impurity A, heat 5 mL of the test solution at 60 °C for 1 h.

Reference solution (c). In order to prepare *in situ* impurity B, expose 5 mL of the test solution to ultraviolet light at 254 nm for 24 h.

Reference solution (d). Dissolve 10.0 mg of *cefuroxime axetil CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

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

Mobile phase: *methanol R*, 23 g/L solution of *ammonium dihydrogen phosphate R* (38:62 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 278 nm.

Injection: 20 µL of the test solution and reference solutions (a), (b) and (c).

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the pair of peaks due to impurity A and use the chromatogram obtained with reference solution (c) to identify the pair of peaks due to impurity B.

Relative retention with reference to cefuroxime axetil diastereoisomer A: cefuroxime axetil diastereoisomer B = about 0.9, impurity A = about 1.2; impurity B = 1.7 and 2.1.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to cefuroxime axetil diastereoisomer A and impurity A.

Limits:

– *impurity A*: maximum 1.5 per cent for the sum of the pair of peaks;
– *impurity B*: maximum 1.0 per cent for the sum of the pair of peaks;
– *impurity E*: maximum 0.5 per cent;
– *any other impurity*: for each impurity, maximum 0.5 per cent;
– *total*: maximum 3.0 per cent;
– *disregard limit*: 0.05 times the area of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

Diastereoisomer ratio. Liquid chromatography (*2.2.29*) as described in the test for related substances.

Limit: test solution:

– the ratio of the area of the peak due to cefuroxime axetil diastereoisomer A to the sum of the areas of the peaks due to cefuroxime axetil diastereoisomers A and B is between 0.48 and 0.55.

Acetone (*2.4.24*): maximum 1.1 per cent.

Water (*2.5.12*): maximum 1.5 per cent, determined on 0.400 g.

ASSAY

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

Injection: test solution and reference solution (d).

System suitability: reference solution (d):

– *resolution*: minimum 1.5 between the peaks due to cefuroxime axetil diastereoisomers A and B;
– *repeatability*: maximum relative standard deviation of 2.0 per cent for the sum of the peaks due to cefuroxime axetil diastereoisomers A and B after 6 injections.

Calculate the percentage content of $C_{20}H_{22}N_4O_{10}S$ from the sum of the areas of the 2 diastereoisomer peaks and the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil CRS*.

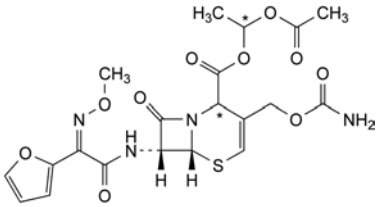
STORAGE

In an airtight container, protected from light.

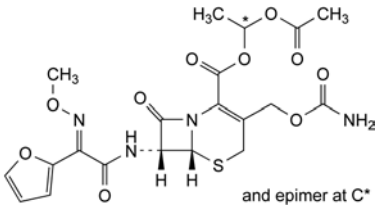
IMPURITIES

Specified impurities: *A, B, E.*

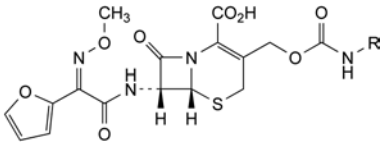
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. 1-(acetyloxy)ethyl (6R,7R)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ^3-isomers),

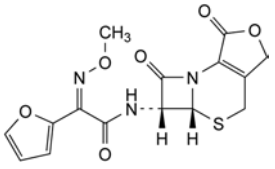


B. (1*RS*)-1-(acetyloxy)ethyl (6*R*,7*R*)-3-[(carbamoyloxy)-methyl]-7-[[(*E*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2carboxylate ((*E*)-isomers),



C. R = CO-CCl_3: (6*R*,7*R*)-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyi-mino)acetyl]amino]-8-oxo-3-[[[(trichloroacetyl)carbamo-yl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

D. R = H: cefuroxime.

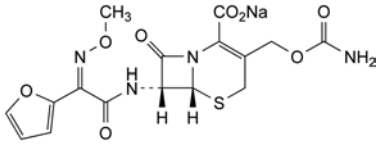


E. (5a*R*,6*R*)-6-[[(2*Z*)-2-(furan-2-yl)-2-(methoxy-imino)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-aze-to[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione (des-carbamoylcefuroxime lactone).

01/2008:0992
corrected 6.0

CEFUROXIME SODIUM

Cefuroximum natricum



$C_{16}H_{15}N_4NaO_8S$ M_r 446.4
[56238-63-2]

DEFINITION

Sodium (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-(furan-2-yl)(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 almost white, slightly hygroscopic powder.

Solubility: freely soluble in water, very slightly soluble in ethanol (96 per cent).

IDENTIFICATION

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

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

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*). The absorbance (*2.2.25*) of solution S measured at 450 nm is not greater than 0.25.

pH (*2.2.3*): 5.5 to 8.5.

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

Specific optical rotation (*2.2.7*): + 59 to + 66 (anhydrous substance).

Dissolve 0.500 g in *acetate buffer solution pH 4.6 R* and dilute to 25.0 mL with the same buffer solution.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or keep at 2-8 °C.*

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

Test solution (b). Dilute 5.0 mL of test solution (a) to 50.0 mL with *water R*.

Reference solution (a). Dissolve 25.0 mg of *cefuroxime sodium CRS* in *water R* and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL to 50.0 mL with *water R*.

Reference solution (b). Place 20 mL of reference solution (a) in a water-bath at 80 °C for 15 min. Cool and inject immediately.

Reference solution (c). Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*.

Column:
– *size*: *l* = 0.125 m, Ø = 4.6 mm;
– *stationary phase*: *hexylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 1 volume of *acetonitrile R* and 99 volumes of an acetate buffer solution pH 3.4, prepared by dissolving 6.01 g of *glacial acetic acid R* and 0.68 g of *sodium acetate R* in *water R* and diluting to 1000 mL with the same solvent.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 273 nm.

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

Run time: 4 times the retention time of cefuroxime.

System suitability: reference solution (b):
– *resolution*: minimum 2.0 between the peaks due to cefuroxime and impurity A.

Limits:
– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);
– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (3.0 per cent);
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 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 3.5 per cent, determined on 0.400 g.

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

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

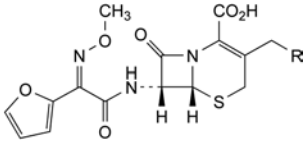
Injection: test solution (b) and reference solution (a).

Calculate the percentage content of cefuroxime sodium.

STORAGE

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

IMPURITIES



A. R = OH: (6*R*,7*R*)-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (descarbamoylcefuroxime),

B. R = O-CO-CH_3: (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

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

D. R = O-CO-NH-CO-CCl_3: (6*R*,7*R*)-7-[[(*Z*)-(furan-2-yl)(methoxyimino)acetyl]amino]-8-oxo-3-[[[(trichloroacetyl)carbamoyl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,