

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

Ethanol (2.4.24). Head-space gas chromatography (2.2.28): use the standard additions method.

Sample solution. Dissolve 0.250 g of the substance to be examined in a mixture of 1 volume of *dimethylacetamide R* and 4 volumes of *water R* and dilute to 25.0 ml with the same mixture of solvents.

Limit:

- *ethanol*: maximum 1.0 per cent *m/m*.

Water (2.5.12): 9.0 per cent to 12.0 per cent, determined on 0.200 g.

Sulphated ash (2.4.14): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

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

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

System suitability: reference solution (a):

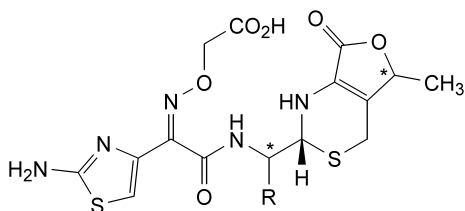
- *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{16}H_{15}N_5O_7S_2$ from the declared content of *cefixime CRS*.

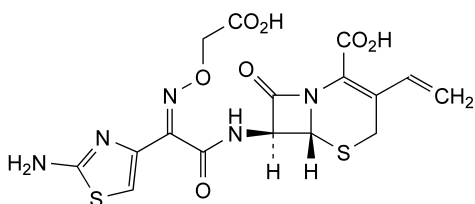
STORAGE

In an airtight container, protected from light.

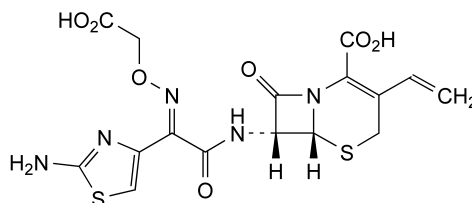
IMPURITIES



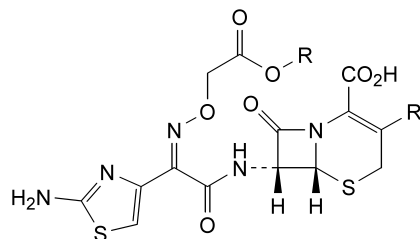
- A. R = CO₂H: 2-[[*Z*]-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-2-[(2*R*)-5-methyl-7-oxo-1,2,5,7-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid,
- B. R = H: 2-[[[*Z*]-1-(2-aminothiazol-4-yl)-2-[[[(2*R*,5*RS*)-5-methyl-7-oxo-1,2,5,7-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl]methyl]amino]-2-oxoethylidene]amino]oxy]acetic acid,



- C. (6*R*,7*S*)-7-[[[*Z*]-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefixime 7-epimer),



- D. (6*R*,7*R*)-7-[[[*E*]-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefixime *E*-isomer),

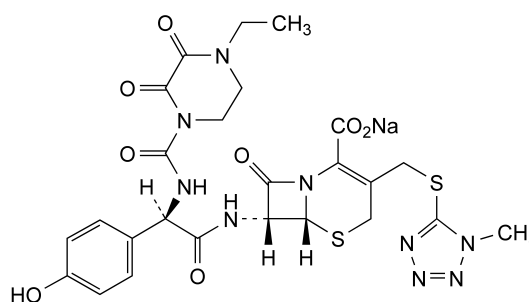


- E. R = H, R' = CH₃: (6*R*,7*R*)-7-[[[*Z*]-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
- F. R = C₂H₅, R' = CH=CH₂: (6*R*,7*R*)-7-[[[*Z*]-2-(2-aminothiazol-4-yl)-2-[(2-ethoxy-2-oxoethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

01/2008:1404
corrected 6.0

CEFOPERAZONE SODIUM

Cefoperazonum natrium



$C_{25}H_{26}N_9NaO_8S_2$
[62893-19-0]

M_r 668

DEFINITION

Sodium (6*R*,7*R*)-7-[[[(2*R*)-2-[[[4-ethyl-2,3-dioxopiperazin-1-yl]carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[[1-methyl-1*H*-tetrazol-5-yl]sulphonyl]methyl]-8-oxo-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 slightly yellow, hygroscopic powder.

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

If crystalline, it shows polymorphism (5.9).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Preparation: dissolve the substance to be examined in *methanol R* and evaporate to dryness. Examine the residue.

Comparison: Ph. Eur. reference spectrum of *cefoperazone sodium*.

B. Examine the chromatograms obtained in the assay.

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

C. It gives reaction (a) of sodium (2.3.1).

TESTS

Appearance of solution. The solution is clear (2.2.1) and its absorbance (2.2.25) at 430 nm is not greater than 0.15.

Dissolve 2.5 g in *water R* and dilute to 25.0 ml with the same solvent.

pH (2.2.3): 4.5 to 6.5.

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent.

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

Test solution (a). Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 250.0 ml with the mobile phase.

Test solution (b). Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 25.0 mg of *cefoperazone dihydrate CRS* in the mobile phase and dilute to 250.0 ml with the mobile phase.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 100.0 ml with the mobile phase.

Column:

- size: $l = 0.15$ m, $\varnothing = 4.6$ mm;
- stationary phase: end-capped octadecylsilyl silica gel for chromatography R (5 μ m).

Mobile phase: mix 884 volumes of *water R*, 110 volumes of *acetonitrile R*, 3.5 volumes of a 60 g/l solution of *acetic acid R* and 2.5 volumes of a triethylammonium acetate solution prepared as follows: dilute 14 ml of *triethylamine R* and 5.7 ml of *glacial acetic acid R* to 100 ml with *water R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 μ l of test solution (b) and reference solutions (a) and (b).

Run time: 2.5 times the retention time of cefoperazone.

Retention time: cefoperazone = about 15 min.

System suitability: reference solution (a):

- number of theoretical plates: minimum 5000, calculated for the principal peak; if necessary, adjust the content of *acetonitrile R* in the mobile phase;
- symmetry factor: maximum 1.6 for the principal peak; if necessary, adjust the content of *acetonitrile R* in the mobile phase.

Limits:

- any impurity: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);
- total: 4.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (4.5 per cent);
- disregard limit: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Acetone (2.4.24, *System B*): maximum 2.0 per cent.

Sample solution. Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 10.0 ml with the same solvent.

Solvent solution. Dissolve 0.350 g of *acetone R* in *water R* and dilute to 100.0 ml with the same solvent. Dilute 10.0 ml of this solution to 100.0 ml with *water R*.

Prepare each of 4 injection vials as shown in the table below:

Vial No.	Sample solution (ml)	Solvent solution (ml)	Water R (ml)
1	1.0	0	4.0
2	1.0	1.0	3.0
3	1.0	2.0	2.0
4	1.0	3.0	1.0

Static head-space conditions which may be used:

- equilibration time: 15 min;
- transfer-line temperature: 110 °C.

Temperature:

- Column: 40 °C for 10 min.

Heavy metals (2.4.8): maximum 5 ppm.

2.0 g complies with test C. Prepare the reference solution using 1 ml of *lead standard solution (10 ppm Pb) R*.

Water (2.5.12): maximum 5.0 per cent, determined on 0.200 g.

Bacterial endotoxins (2.6.14): less than 0.20 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

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

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

System suitability: reference solution (a):

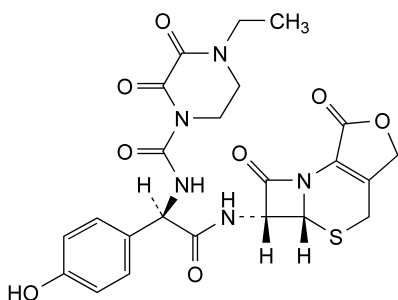
- repeatability: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of cefoperazone sodium by multiplying the percentage content of cefoperazone by 1.034.

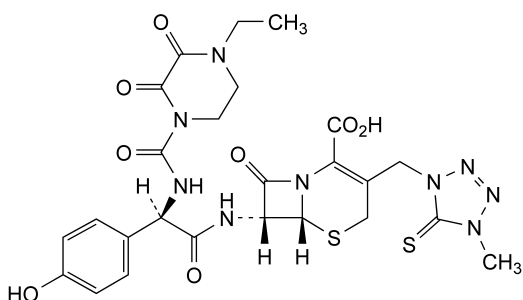
STORAGE

In an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

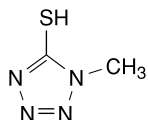
IMPURITIES



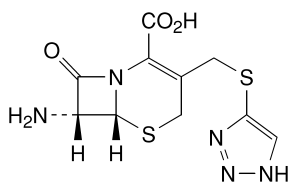
- A. (5a*R*,6*R*)-6-[[[(2*R*)-2-[[[(4-ethyl-2,3-dioxopiperazin-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



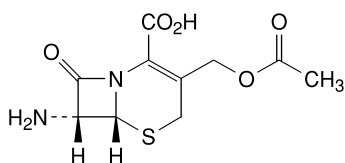
- B. (6*R*,7*R*)-7-[[[(2*R*)-2-[[[(4-ethyl-2,3-dioxopiperazin-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[4-methyl-5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



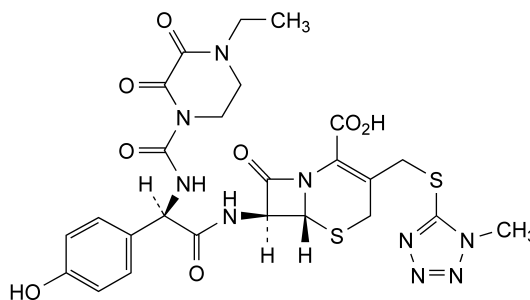
- C. 1-methyl-1*H*-tetrazole-5-thiol,



- D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*H*-1,2,3-triazol-4-yl)sulphonyl)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),

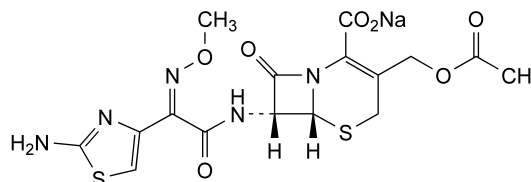


- F. (6*R*,7*S*)-7-[[[(2*R*)-2-[[[(4-ethyl-2,3-dioxopiperazine-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[1-methyl-1*H*-tetrazol-5-yl)sulphonyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

01/2008:0989

CEFOTAXIME SODIUM

Cefotaximum natricum


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

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.