Temperature:
– *column*: 200 °C;
– *injection port and detector*: 250 °C.
Detection: flame ionisation.
Injection: 1 µL of the test solution and reference solution (b).
Limit:
– *propylene glycol*: 13.0 per cent to 18.0 per cent.

Related substances. Liquid chromatography (*2.2.29*).
Test solution. Dissolve 60.0 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 60.0 mg of *cefatrizine propylene glycol CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.
Reference solution (b). Dissolve 30.0 mg of *cefatrizine impurity A CRS* in *buffer solution pH 7.0 R* and dilute to 100.0 mL with the same buffer solution.
Reference solution (c). Dilute 0.6 mL of reference solution (a) to 100.0 mL with the mobile phase.
Reference solution (d). Dilute 1.0 mL of reference solution (b) to 100.0 mL with *buffer solution pH 7.0 R*.
Reference solution (e). To 1.0 mL of reference solution (a) add 1.0 mL of reference solution (b) and dilute to 10.0 mL with the mobile phase.
Column:
– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).
Mobile phase: mix 5 volumes of *acetonitrile R* and 95 volumes of a 2.72 g/L solution of *potassium dihydrogen phosphate R* in *water R*.
Flow rate: 2 mL/min.
Detection: spectrophotometer at 272 nm.
Injection: 20 µL of the test solution and reference solutions (c), (d) and (e).
Run time: at least twice the retention time of cefatrizine.
System suitability: reference solution (e):
– *resolution*: minimum 5.0 between the peaks due to cefatrizine and impurity A.
Limits:
– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.5 per cent);
– *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent);
– *sum of impurities other than A*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.1 per cent);
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.03 per cent).

Water (*2.5.12*): maximum 1.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

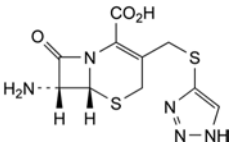
ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.
Injection: 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 $C_{18}H_{18}N_6O_5S_2$ from the declared content of $C_{18}H_{18}N_6O_5S_2$ in *cefatrizine propylene glycol CRS*.

IMPURITIES

Specified impurities: A.

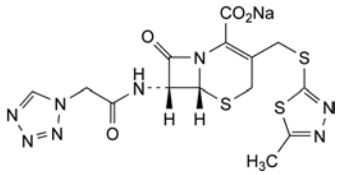


A. (6*R*,7*R*)-7-amino-8-oxo-3-[[(1*H*-1,2,3-triazol-4-yl)sulfanyl]-methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA triazole).

01/2008:0988
corrected 6.0

CEFAZOLIN SODIUM

Cefazolinum natricum



$C_{14}H_{13}N_8NaO_4S_3$ M_r 476.5
[27164-46-1]

DEFINITION

Sodium (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)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: freely soluble in water, very slightly soluble in ethanol (96 per cent).
It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: dissolve 0.150 g in 5 mL of *water R*, add 0.5 mL of *dilute acetic acid R*, swirl and allow to stand for 10 min in iced water. Filter the precipitate and rinse with 1-2 mL of *water R*. Dissolve in a mixture of 1 volume of *water R* and 9 volumes of *acetone R*. Evaporate the solvent almost to dryness, then dry in an oven at 60 °C for 30 min.
Comparison: *cefazolin 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 25.0 mL with the same solvent.

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

pH (*2.2.3*): 4.0 to 6.0 for solution S.

Specific optical rotation (*2.2.7*): – 15 to – 24 (anhydrous substance).
Dissolve 1.25 g in *water 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 272 nm. The specific absorbance at the maximum is 260 to 300 (anhydrous substance).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with the same mobile phase.

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

Reference solution (b). Dissolve 20 mg of the substance to be examined in 10 mL of a 2 g/L solution of *sodium hydroxide R*. Allow to stand for 15-30 min. Dilute 1.0 mL of the solution to 20 mL with mobile phase A.

Column:

- *size*: *l* = 0.125 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm);
- *temperature*: 45 °C.

Mobile phase:

- *mobile phase A*: solution containing 14.54 g/L of *disodium hydrogen phosphate R* and 3.53 g/L of *potassium dihydrogen phosphate 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 - 2	98	2
2 - 4	98 → 85	2 → 15
4 - 10	85 → 60	15 → 40
10 - 11.5	60 → 35	40 → 65
11.5 - 12	35	65
12 - 15	35 → 98	65 → 2
15 - 21	98	2

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 5 µL.

System suitability: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to cefazolin and impurity L (see Figure 0988.-1).

Limits:

- *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.5 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).

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

Water (*2.5.12*): maximum 6.0 per cent, determined on 0.300 g.

Bacterial endotoxins (*2.6.14*): less than 0.15 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 50.0 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 50.0 mg of *cefazolin CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *cefuroxime sodium CRS* in 10.0 mL of reference solution (a) and dilute 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: mix 10 volumes of *acetonitrile R* and 90 volumes of a solution containing 2.77 g/L of *disodium hydrogen phosphate R* and 1.86 g/L of *citric acid R*.

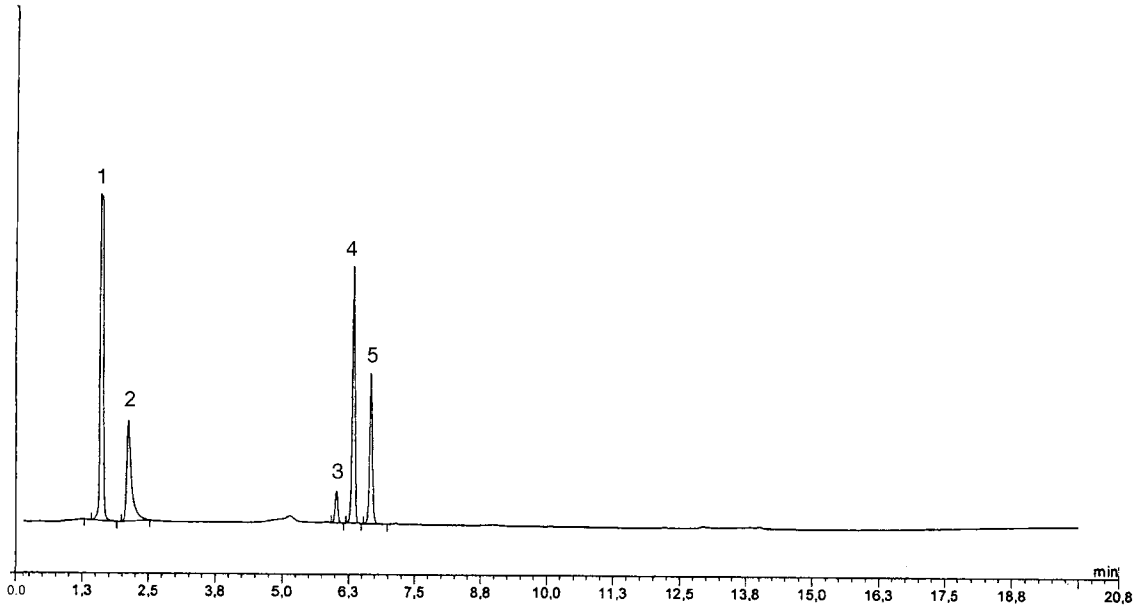
Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 270 nm.

Injection: 20 µL.

System suitability: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to cefazolin and cefuroxime.



1. impurity J
2. impurity E
3. unknown
4. cefazolin
5. impurity L

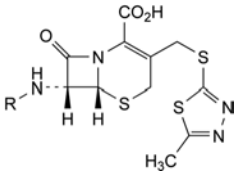
Figure 0988.-1. – *Chromatogram for the test for related substances of cefazolin sodium: reference solution (b) (in situ degradation)*

Calculate the percentage content of cefazolin sodium by multiplying the percentage content of cefazolin by 1.048.

STORAGE

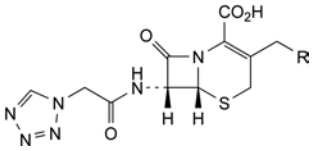
In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES



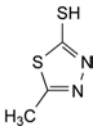
A. R = H: (6*R*,7*R*)-7-amino-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

B. R = CO-C(CH_3)$_3$: (6*R*,7*R*)-7-[(2,2-dimethylpropanoyl)amino]-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

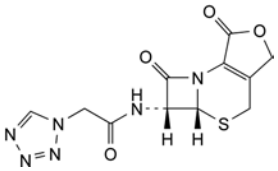


C. R = H: (6*R*,7*R*)-3-methyl-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

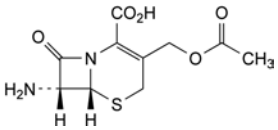
D. R = O-CO-CH_3: (6*R*,7*R*)-3-[(acetyloxy)methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



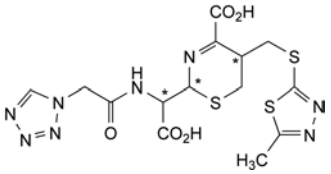
E. 5-methyl-1,3,4-thiadiazol-2-thiol (MMTD),



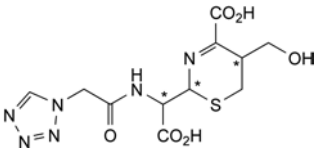
G. (5a*R*,6*R*)-6-[(1*H*-tetrazol-1-ylacetyl)amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione,



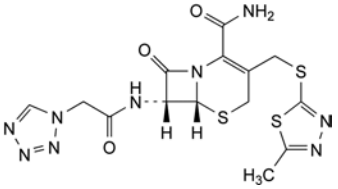
H. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA),



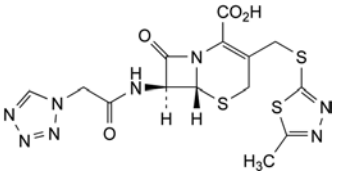
I. 2-[carboxy[(1*H*-tetrazol-1-ylacetyl)amino]methyl]-5-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid (cefazoloic acid),



J. 2-[carboxy[(1*H*-tetrazol-1-ylacetyl)amino]methyl]-5-(hydroxymethyl)-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid (hydrolysed cefazoloic acid),



K. (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamide (cefazolinamide),

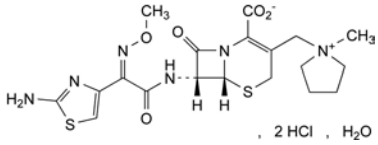


L. (6*R*,7*S*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

01/2008:2126

CEFEPIME DIHYDROCHLORIDE MONOHYDRATE

Cefepimi dihydrochloridum monohydricum



$C_{19}H_{26}Cl_2N_6O_5S_2,H_2O$ M_r 571.5

[123171-59-5]

DEFINITION

(6*R*,7*R*)-7-[[(2*Z*)-(2-Aminothiazol-4-yl)(methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate dihydrochloride monohydrate. Semi-synthetic product derived from a fermentation product.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefepime dihydrochloride monohydrate CRS*.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_3 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.