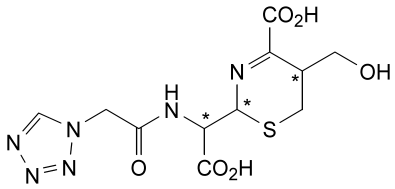
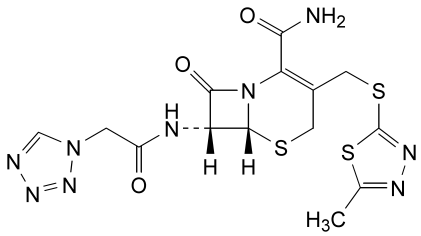
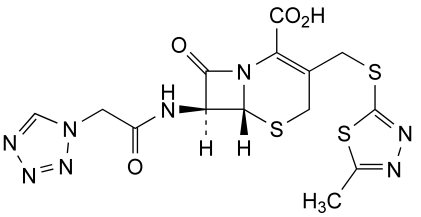


J. 2-[carboxy[(1*H*-tetrazol-1-ylacetyl)amino]methyl]-5-(hydroxymethyl)-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid (hydrolysed cefazoloic acid),



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

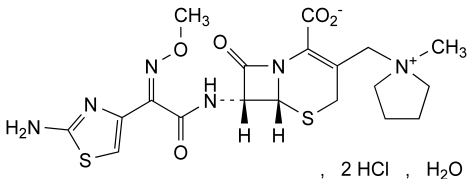


L. (6*R*,7*S*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)sulphanyl]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

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.

Specific optical rotation (*2.2.7*): + 40 to + 45 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 ml with the same solvent.

Impurity G. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in *0.01 M nitric acid* and dilute to 10.0 ml with the same acid.

Reference solution (a). Dilute 0.250 g of *N-methylpyrrolidine R* (impurity G) to 100.0 ml with *water R*. Dilute 2.0 ml of this solution to 100.0 ml with *0.01 M nitric acid*.

Reference solution (b). Dilute 0.250 g of *pyrrolidine R* to 100 ml with *0.01 M nitric acid*. Dilute 2 ml of the solution to 100 ml with *0.01 M nitric acid*. Mix 5 ml of this solution with 5 ml of reference solution (a).

Column:
– *size*: *l* = 0.05 m, Ø = 4.6 mm;
– *stationary phase*: *strong cation-exchange resin R* (5 µm).

Mobile phase: mix 1 volume of *acetonitrile R* and 100 volumes of *0.01 M nitric acid*; filter through a 0.2 µm filter.

Flow rate: 1 ml/min.

Detection: conductivity detector.

Injection: 100 µl.

Run time: 1.1 times the retention time of cefepime (retention time = about 50 min, eluting as a broadened peak).

System suitability:
– *symmetry factor*: maximum 2.5 for the peak due to impurity G in the chromatogram obtained with reference solution (a);
– *repeatability*: maximum relative standard deviation of 5.0 per cent after 6 injections of reference solution (a);
– *peak-to-valley ratio*: minimum 3 between the peaks due to pyrrolidine and impurity G in the chromatogram obtained with reference solution (b).

Calculate the percentage content of impurity G in the test solution using reference solution (a).

Limit:
– *impurity G*: maximum 0.5 per cent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use or keep refrigerated at 4-8 °C for not more than 12 h.*

Test solution. Dissolve 70.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 ml with mobile phase A. Sonicate for 30 s and stir for about 5 min.

Reference solution (a). Dissolve 70.0 mg of *cefepime dihydrochloride monohydrate CRS* in mobile phase A and dilute to 50.0 ml with mobile phase A. Sonicate for 30 s and stir for about 5 min.

Reference solution (b). Dilute 1.0 ml of the test solution to 10.0 ml with mobile phase A. Dilute 2.0 ml of this solution to 100.0 ml with mobile phase A.

Reference solution (c). Dissolve 7 mg of *cefepime dihydrochloride monohydrate for system suitability CRS* (containing impurities A, B, E and F) in mobile phase A and dilute to 5 ml with mobile phase A.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase:

– *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of a 0.68 g/l solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *0.5 M potassium hydroxide*;

– *mobile phase B*: mix equal volumes of *acetonitrile R* and a 0.68 g/l solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *0.5 M potassium hydroxide*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 30	100 → 50	0 → 50
30 - 35	50	50
35 - 36	50 → 100	50 → 0
36 - 45	100	0

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl of the test solution and reference solutions (b) and (c).

Identification of impurities: use the chromatogram supplied with *cefepime dihydrochloride monohydrate for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B, E and F.

Relative retention with reference to cefepime (retention time = about 7 min): impurity E = about 0.4; impurity F = about 0.8; impurity A = about 2.5; impurity B = about 4.1.

System suitability: reference solution (c):

– *resolution*: minimum 1.5 between the peaks due to impurity F and cefepime.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.4; impurity B = 1.4; impurity E = 1.8;

– *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

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

– *impurity E*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 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 (b) (0.10 per cent);

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

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): 3.0 per cent to 4.5 per cent, determined on 0.400 g.

Bacterial endotoxins (*2.6.14*): less than 0.04 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.

Mobile phase: mobile phase A.

Injection: test solution and reference solution (a).

Run time: 1.4 times the retention time of cefepime.

Calculate the percentage content of $C_{19}H_{26}Cl_2N_6O_5S_2$ from the declared content of *cefepime dihydrochloride monohydrate CRS*.

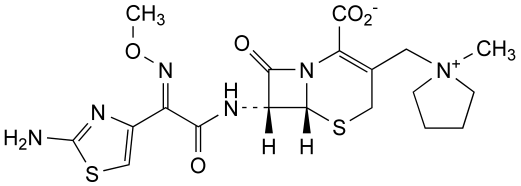
STORAGE

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

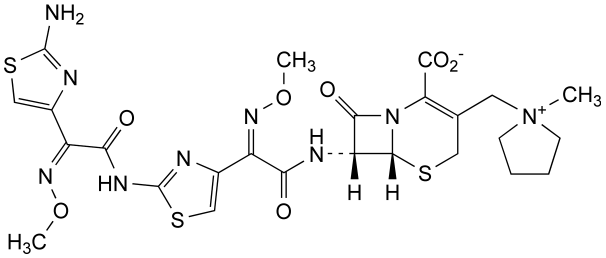
IMPURITIES

Specified impurities: A, B, E, F, G.

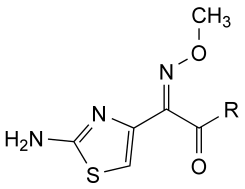
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. (6*R*,7*R*)-7-[[(2*E*)-(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 (*anti*-cefepime),

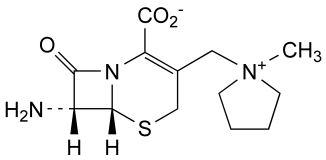


B. (6*R*,7*R*)-7-[[(2*Z*)-[2-[[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino]thiazol-4-yl](methoxyimino)acetyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

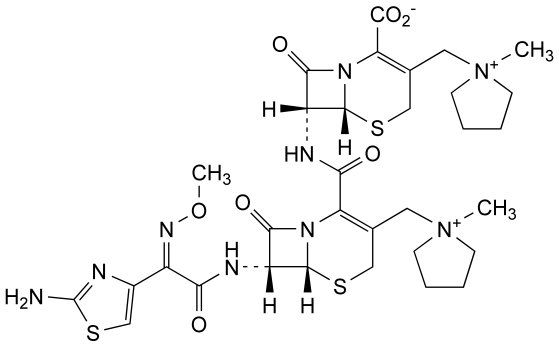


C. R = NH-CH_2-CHO: (2*Z*)-2-(2-aminothiazol-4-yl)-*N*-(formylmethyl)-2-(methoxyimino)acetamide,

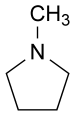
D. R = OH: (2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetic acid,



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



F. (6*R*,7*R*)-7-[[[(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-en-2-yl]carbonyl]amino]-3-[(1-methylpyrrolidinio)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

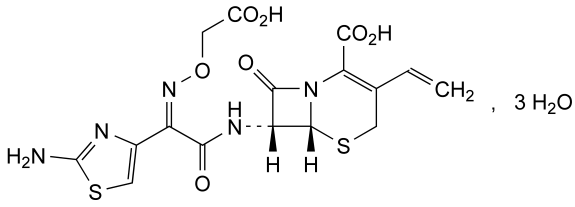


G. *N*-methylpyrrolidine.

01/2008:1188
corrected 6.0

CEFIXIME

Cefiximum



$C_{16}H_{15}N_5O_7S_2,3H_2O$ M_r 507.5

DEFINITION

(6*R*,7*R*)-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 trihydrate.

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, slightly hygroscopic powder.

Solubility: slightly soluble in water, soluble in methanol, sparingly soluble in anhydrous ethanol, practically insoluble in ethyl acetate.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cefixime CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

pH (*2.2.3*): 2.6 to 4.1.

Suspend 0.5 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent.

Related substances. 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 *cefixime CRS* in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the mobile phase.

Reference solution (c). Dissolve 10 mg of *cefixime CRS* in 10 ml of *water R*. Heat on a water-bath for 45 min and cool (*in situ* preparation of impurity D). Inject immediately.

Column:

- *size*: *l* = 0.125 m, Ø = 4 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 40 °C.
- *Mobile phase*: mix 250 volumes of *acetonitrile R* and 750 volumes of a tetrabutylammonium hydroxide solution prepared as follows: dissolve 8.2 g of *tetrabutylammonium hydroxide R* in *water R* and dilute to 800 ml with the same solvent; adjust to pH 6.5 with *dilute phosphoric acid R* and dilute to 1000 ml with *water R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl of the test solution and reference solutions (b) and (c).

Run time: 3 times the retention time of cefixime.

System suitability: reference solution (c):

- *resolution*: minimum 2.0 between the peaks due to cefixime and impurity D; if necessary, adjust the concentration of acetonitrile in the mobile phase.

Limits:

- *any impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3 per cent);