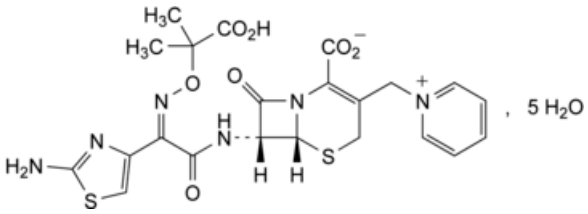
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ceftazidime Pentahydrate

General Notices

Ceftazidime

(Ph. Eur. monograph 1405)



$C_{22}H_{22}N_6O_7S_2,5H_2O$ 637 *78439-06-2*

Action and use

Cephalosporin antibacterial.

Preparations

Ceftazidime Eye Drops

Ceftazidime for Injection

Ceftazidime Injection

Ph Eur

DEFINITION

(6*R*,7*R*)-7-[[(2*Z*)-2-(2-Aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate.

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, crystalline powder.

Solubility

Slightly soluble in water and in methanol, practically insoluble in acetone and in ethanol (96 per cent). It dissolves in acid and alkali solutions.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ceftazidime CRS*.

TESTS

Solution S

Dissolve 0.25 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

3.0 to 4.0 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Suspend 0.150 g of the substance to be examined in 5 mL of *acetonitrile R*, dissolve by adding *water R* and dilute to 100 mL with *water R*.

Reference solution (a) To 1.0 mL of the test solution add 5.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 5.0 mL with *water R*.

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

Reference solution (c) Dissolve the contents of a vial of *ceftazidime for peak identification CRS* (containing impurities A and G) in 2.0 mL of *water R*.

Column:

— *size*: *l* = 0.25 m, *Ø* = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: solution containing 3.6 g/L of *disodium hydrogen phosphate dodecahydrate R* and 1.4 g/L of *potassium dihydrogen phosphate R*, adjusted to pH 3.4 with a 10 per cent *V/V* solution of *phosphoric acid 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 - 4	96 → 89	4 → 11

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
4 - 5	89	11
5 - 8	89 → 84	11 → 16
8 - 11	84 → 80	16 → 20
11 - 15	80 → 50	20 → 50
15 - 18	50 → 20	50 → 80
18 - 22	20	80

Flow rate 1.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Relative retention With reference to ceftazidime (retention time = about 8 min): impurity F = about 0.4; impurity G = about 0.8; impurity A = about 0.9; impurity B = about 1.4.

Identification of impurities Use the chromatogram supplied with *ceftazidime for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and G; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

System suitability Reference solution (c):

— *resolution*: minimum 4.0 between the peaks due to impurity A and ceftazidime.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity G by 3.0;

— *impurities A, B, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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 (a) (0.10 per cent);

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

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard the peak due to impurity F.

Impurity F

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

Phosphate buffer solution Prepare a 10 per cent *V/V* solution of *phosphate buffer solution pH 7.0 R4*.

Test solution Dissolve 0.500 g of the substance to be examined in phosphate buffer solution and dilute to 100.0 mL with the same solution.

Reference solution (a) Dissolve 1.00 g of *pyridine R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 200.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with phosphate buffer solution.

Reference solution (b) Dilute 1 mL of the test solution to 200 mL with phosphate buffer solution. To 1 mL of this solution add 20 mL of reference solution (a) and dilute to 200 mL with phosphate buffer solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 8 volumes of a 28.8 g/L solution of *ammonium dihydrogen phosphate R* previously adjusted to pH 7.0 with *ammonia R*, 24 volumes of *acetonitrile R* and 68 volumes of *water R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 255 nm.

Injection 20 µL.

Run time 10 min.

System suitability Reference solution (b):

— *resolution*: minimum 7.0 between the peaks due to ceftazidime and impurity F.

Limit:

— *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (500 ppm).

Water (*2.5.12*)

13.0 per cent to 15.0 per cent, determined on 0.100 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*).

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 *ceftazidime CRS* in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *ceftazidime for peak identification CRS* (containing impurities A and G) in 3.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *hexylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 4.3 g of *disodium hydrogen phosphate dodecahydrate R* and 2.7 g of *potassium dihydrogen phosphate R* in 980 mL of *water R*, then add 20 mL of *acetonitrile R*.

Flow rate 2 mL/min.

Detection Spectrophotometer at 245 nm.

Injection 20 µL.

Run time 6 min.

Relative retention With reference to ceftazidime (retention time = about 4.5 min): impurity A = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity A and ceftazidime.

Calculate the content of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) taking into account the assigned content of $C_{22}H_{22}N_6O_7S_2$ in *ceftazidime CRS*.

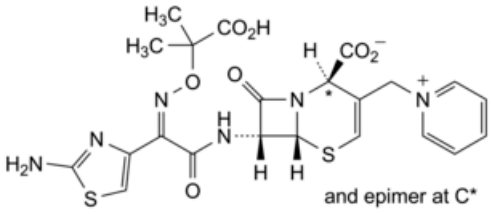
STORAGE

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

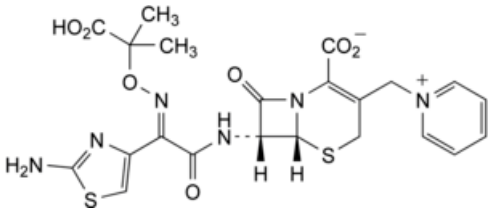
IMPURITIES

Specified impurities A, B, F, G.

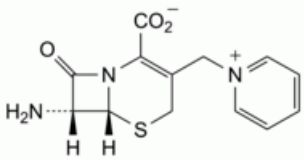
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



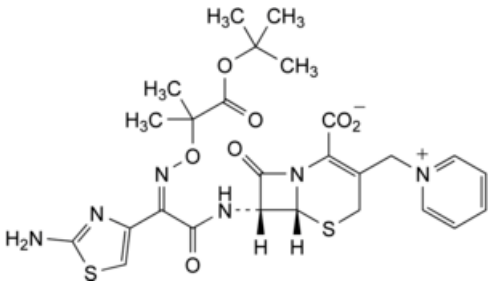
A. (2*RS*,6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ-2-ceftazidime),



B. (6*R*,7*R*)-7-[[(2*E*)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

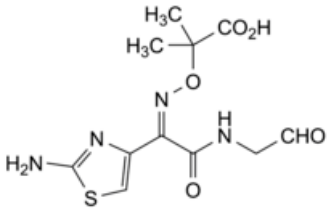


C. (6*R*,7*R*)-7-amino-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

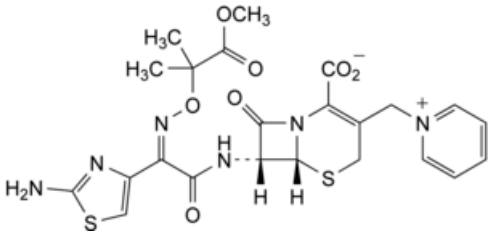


E. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,

F. pyridine,



G. 2-[[[(1*Z*)-1-(2-aminothiazol-4-yl)-2-[(oxoethyl)amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoic acid,



H. (6*R*,7*R*)-7-[[(2*Z*)-2-(2-aminothiazol-4-yl)-2-[(2-methoxy-1,1-dimethyl-2-oxoethoxy)imino]acetyl]amino]-8-oxo-3-[(pyridin-1-ium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

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