Cefprozil

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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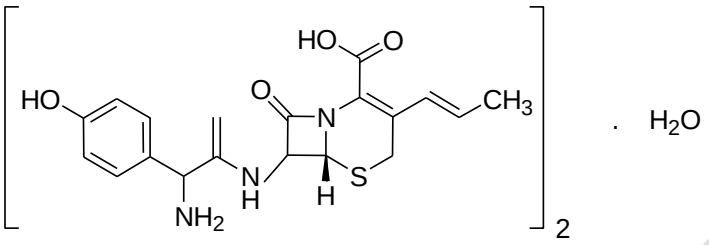
Cefprozil



$C_{18}H_{19}N_3O_5S.H_2O$ Mol. Wt. 407.4

Cefprozil is 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-(1-propenyl)-, monohydrate, [6R-[6α,7β(R*)]].

Cefprozil contains not less than 900 µg and not more than 1050 µg of $C_{18}H_{19}N_3O_5S$, per mg, calculated on the anhydrous basis.

Category. Antibacterial

Description. A white to off-white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cefprozil IPRS* or with the reference spectrum of cefprozil.

B. In the Assay, the principal peaks in the chromatogram obtained with the test solution correspond to the peak in the chromatogram obtained with reference solution (a) and (b).

Tests

Related substances.

A. Determine by liquid chromatography (2.4.14). *(When the impurity profile includes Z-cefprozil open ring, E-cefprozil open ring, and cefprozil related compound K)*

Test solution. Dissolve 250 mg of the substance under examination in 2 ml of *1M hydrochloric acid* and dilute to 50.0 ml with mobile phase A. (*Store the solution at 4° and use within 3 Hour).*

Reference solution (a). Dissolve 2.5 mg, each of, *cefprozil (Z)-Isomer IPRS, amoxicillin related compound I IPRS,* and *cefprozil related compound D IPRS* in 2 ml of *1M hydrochloric acid* and dilute to 10.0 ml with mobile phase A. Dilute 5.0 ml of the solution to 25.0 with mobile phase A. *(Store the solution at 4° and use within 12 Hour).*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 with mobile phase A. (*Store the solution at 4°, and use within 8 Hr).*

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hydrosphere C18),
- column temperature: 40°,
- sample temperature: 4°,
- mobile phase: A. a buffer solution prepared by dissolving 11.5 g of *ammonium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 4.4 with *orthophosphoric acid*,
  B. a mixture of equal volumes of *acetonitrile* and mobile phase A,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 230 nm,

– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	81	19
8	81	19
20	36	64
25	36	64
27	81	19
30	81	19

[NOTE: These gradient elution times are established on an HPLC system with a dwell volume of approximately 1.3 ml. The specified gradient elution times can be adjusted as necessary to achieve the separation described]

Name	Relative retention time
Amoxicillin related compound I[1]	0.40
Cefadroxil	0.54
Hydroxyphenyldiketopiperazine[2]	0.61
Cefprozil related compound D (Z)-isomer[3*]	0.69
O-Acyl cefprozil[4]	0.76
Cefprozil related compound D (E)-isomer[5]	0.91
Cefprozil (Z)-isomer	1.0
Cefprozil (E)-isomer	1.37
Z-Cefprozil open ring[6]	1.74
Cefprozil related compound H (Z)-isomer[7#]	1.95
E-Cefprozil open ring[8]	2.08
Cefprozil related compound H (E)-isomer[9]	2.19
Cefprozil related compound K[10@]	2.76, 2.86, 2.91, 3.01

[*]The sum of the two isomers is reported.
[#]The sum of the two isomers is reported.
[@] The system resolves four isomers of cefprozil related compound K.

[1](R)-2-Amino-2-(4-hydroxyphenyl)acetic acid,
[2]3-(Aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione,
[3]7-Amino-3-propenylcephalosporanic acid (Z-isomer); (6R,7R)-7-Amino-8- oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[4](6R,7R)-7-[(R)-2-Amino-2-{4-[(R)-2-amino-2-(4-hydroxyphenyl)acetoxy]phenyl}acetamido]-8-oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[5]7-Amino-3-propenylcephalosporanic acid (E-isomer); (6R,7R)-7-Amino-8-oxo-3-[(E)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[6](R)-2-{(R)-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5-[(Z)-prop-1-enyl]-3,6-dihydro-2H-1,3-thiazine-4-carboxylic acid,
[7]N-Acyl cefprozil (Z-isomer); (6R,7R)-7-{(R)-2-[(R)-2-Amino-2-(4- hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-8-oxo-3-[(Z)- prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[8]prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylicacid.k(R)-2-{(R)-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5-[(E)-prop-1-enyl]-3,6-dihydro-2H-1,3-thiazine-4-carboxylic acid,
[9]N-Acyl cefprozil (E-isomer); (6R,7R)-7-{(R)-2-[(R)-2-Amino-2-(4- hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-8-oxo-3-[(E)- prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[10]Hydroxyphenyldiketopiperazine lactone; 3-(5-Ethyl-7-oxo-2,4,5,7-tetrahydro1H-furo[3,4-d][1,3]thiazin-2-yl)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to (E)-isomer of cefprozil related compound D and cefprozil (Z)-isomer is not less than 1.4 and the relative standard deviation for replicate injections is not more than 10.0 per cent for each peak in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 10 for each peak in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to amoxicillin related compound I is not more than 0.3 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the sum of the areas of the peaks corresponding to cefprozil related compound D (Z)-isomer and cefprozil related compound D (E)-isomer is not more than 0.3 times the area of the cefprozil related compound D (Z)-isomer peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to hydroxyphenyldiketopiperazine is not more than 0.3 times the area of the principal peak (cefprozil (Z)-isomer peak) in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to cefadroxil is not more than 0.5 times the area of the principal peak in the chromatogram

obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to o-acyl cefprozil, Z-cefprozil open ring, each of, is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 percent), the sum of the areas of the peaks corresponding to cefprozil related compound H (Z)-isomer and cefprozil related compound H (E)-isomer is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to cefprozil related compound K isomer at RRT 2.76, 2.86, 2.91 and 3.01, each of, is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

B. Determine by liquid chromatography (2.4.14). *(When the impurity profile includes ethoxycarbonyl cefprozil, methoxycefadroxil, cefprozil delta-3 isomer, cefprozil amide, and cefprozil dimer.)*

Solvent mixture. Dissolve 0.85 g of *potassium dihydrogen phosphate* and 1.16 g of *anhydrous disodium hydrogen phosphate* in 1000 ml *water*.

Test solution. Dissolve 150 mg of the substance under examination in mobile phase A and dilute to 100.0 ml with mobile phase A. (*Refrigerate the solution, and use within 1 hour).*

Reference solution (a). Dissolve 1.5 mg of *cefadroxil IPRS* and 7.5 mg of *cefprozil related compound D IPRS* in 2 ml of mobile phase A and dilute to 10.0 ml with the solvent mixture.

Reference solution (b). a 0.15 per cent w/v solution of *cefprozil IPRS* in mobile phase A.

Reference solution (c). Dilute 1.0 ml reference solution (a) to 10.0 ml with reference solution (b).

Reference solution (d). Dilute 1.0 ml reference solution (b) to 100.0 ml with mobile phase A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm)
- column temperature: 30°
- sample temperature: 4°,
- mobile phase: A. a buffer solution prepared by dissolving 4 g of *sodium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 4.2 with dilute *orthophosphoric acid*,
  B. a mixture of equal volumes of *acetonitrile* and mobile phase A,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
20	70	30
40	40	60
50	0	100
60	0	100
62	95	5
70	95	5

Name	Relative retention time	Correction factor
Amoxicillin related compound I[1]	0.17	0.67
Cefprozil related compound D (Z)-isomer[2]	0.57	1.79
Cefadroxil	0.62	0.91
Methoxycefadroxil[3]	0.65	2.27
Cefprozil related compound D (E)-isomer[4]	0.73	1.79

Cefprozil delta-3 isomer[5]	0.92	1.05
Cefprozil (Z)-isomer	1.0	-
Cefprozil (E)-isomer	1.17	-
Cefprozil related compound D (H)-isomer[6]	1.33	1.08
Cefprozil amide[7]	1.46	1.11
Ethoxycarbonyl-cefprozil	2.08	1.43
Cefprozil dimer[8]	2.21	1.11

[1](R)-2-Amino-2-(4-hydroxyphenyl)acetic acid,
[2]7-Amino-3-propenylcephalosporanic acid (Z-isomer); (6R,7R)-7-Amino-8- oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[3](6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-(methoxymethyl)- 8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[4]7-Amino-3-propenylcephalosporanic acid (E-isomer); (6R,7R)-7-Amino-8-oxo-3-[(E)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[5](6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid,
[6]N-Acyl cefprozil (Z-isomer); (6R,7R)-7-{(R)-2-[(R)-2-Amino-2-(4- hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-8-oxo-3-[(Z)- prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[7](R)-2-{(6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamido}-2-(4-hydroxyphenyl)acetic acid,
[8](6R,7R)-7-{(R)-2-Amino-2-[4-(ethoxycarbonyloxy)phenyl]acetamido}-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,
[9](6R,7R)-7-[(R)-2-{(6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2- carboxamido}-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]- 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Inject reference solution (c) and (d). The test is not valid unless the resolution between the peaks due to (Z)-isomer of cefprozil related compound D and cefprozil is not less than 1.5 in the chromatogram obtained with reference solution (c), the relative standard deviation for replicate injections is not more than 5.0 per cent, for the sum of cefprozil (Z)-isomer and cefprozil (E)-isomer in the chromatogram obtained with reference solution (d).

Injection reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to amoxicillin related compound I, methoxycefadroxil, cefprozil related compound H, cefprozil amide and ethoxycarbonylcefprozil, each of, is not more than 0.15 times of sum of the areas of cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (0.15 per cent), the area of any peak corresponding to cefadroxil is not more than sum of areas of the cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (1.0 per cent), the area of any peak corresponding to cefprozil related compound D (Z) isomer and cefprozil related compound D (E) isomer, each of, is not more than 0.3 times the sum of the areas of cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (0.3 per cent), the area of any peak corresponding to cefprozil delta-3 isomer and cefprozil dimer is not more than 0.2 times the sum of the areas of cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the area of any other secondary peak is not more than 0.2 times the sum of the areas of cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (0.2 per cent), the sum of areas of all the secondary peaks is not more than twice the area of the sum of the areas of the cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (2.0 per cent). Ignore any peak with an area 0.05 times the sum of the areas of cefprozil (Z) isomer and cefprozil (E) isomer peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

pH (2.4.24). 3.5 to 6.5, determined in a 0.5 percent w/v solution in *water*.

Water (2.3.43). 3.5 per cent to 6.5 per cent.

Assay. Determine by liquid chromatography (2.4.14)

Note- Use these solutions within 6 hour)

Test solution. Dissolve 30 mg of the substance under examination in *water* and dilute to 100.0 with *water.*

Reference solution (a). A 0.025 per cent w/v solution of *cefprozil (Z)-isomer IPRS* in *water*.

Reference solution (b). A 0.0025 per cent w/v solution of *cefprozil (E)-isomer IPRS* in *water*.

Reference solution (c). A solution containing 0.0125 per cent, each of *cefprozil (Z)-isomer IPRS* and *cefprozil (E)-isomer IPRS* in *water*.

Chromatographic system

– a stainless steel column 30 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
– mobile phase: a mixture of 90 volumes of a buffer solution prepared by dissolving 11.5 g of *ammonium dihydrogen phosphate* in *water*, adjusted to pH 4.4 with *orthophosphoric acid* and 10 volumes of *acetonitrile*,

– flow rate: 1 ml per minute,
– spectrophotometer set at 280 nm,
– injection volume: 10 µl.

The Relative retention time with reference to cefprozil (E) isomer for cefprozil (Z) isomer is about 0.7.

Inject reference solution (a), (c) and the test solution. The test is not valid unless the resolution between the peaks due to cefprozil (Z)-isomer and cefprozil (E)-isomer is not less than 2.5 in the chromatogram obtained with reference solution (c), the tailing factor is between 0.9 to 1.1 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) (for Z-isomer), (b) (for E-isomer) and the test solution.

Calculate the content of Cefprozil, $C_{18}H_{19}N_3O_5S$ (in µg/mg) by adding the values of cefprozil (Z) isomer (in µg/mg) and cefprozil (E) isomer (in µg/mg).

Cefprozil (E)-Isomer ratio. Between 0.06-0.11, calculate the cefprozil (E)-isomer ratio using chromatograms of reference solution (a), reference solution (b) and the test solution obtained under Assay.

$$\text{Cefprozil (E)-isomer ratio} = \frac{E}{E+Z}$$

Where,

E= content of cefprozil (E) isomer, determined in assay (µg/mg),

Z= content of cefprozil (Z) isomer, determined in assay (µg/mg).

Storage. Store protected from moisture, at a temperature not exceeding 30°.

Labelling. If a test for Related substances other than Related substances A is used, the labelling states the test with which the article complies.