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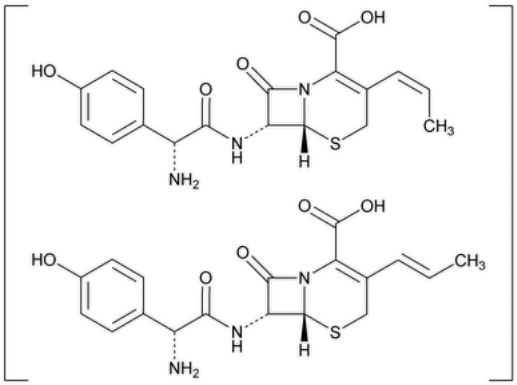
Cefprozil



• H_2O

$C_{18}H_{19}N_3O_5S \cdot H_2O$ 407.44

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, [6*R*-[6α,7β(*R**)]]-;

(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate CAS RN®: 121123-17-9.

Anhydrous 389.43 CAS RN®: 92665-29-7.

DEFINITION

Cefprozil contains NLT 900 µg/mg and NMT 1050 µg/mg of cefprozil ($C_{18}H_{19}N_3O_5S$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (CN 1-May-2020)

• **B.** The retention times of the cefprozil (*Z*)-isomer and cefprozil (*E*)-isomer peaks from the *Sample solution* correspond to those of the Standard solutions, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 11.5 g/L of monobasic ammonium phosphate in water. Adjust, if necessary, with phosphoric acid to a pH of 4.4.

Mobile phase: Acetonitrile and *Buffer* (100:900)

System suitability solution: 0.125 mg/mL each of USP Cefprozil (*Z*)-Isomer RS and USP Cefprozil (*E*)-Isomer RS in water. Use this solution within 6 h.

Standard solution 1: 0.25 mg/mL of USP Cefprozil (*Z*)-Isomer RS in water. Use this solution within 6 h.

Standard solution 2: 0.025 mg/mL of USP Cefprozil (*E*)-Isomer RS in water. Use this solution within 6 h.

Sample solution: 0.3 mg/mL of Cefprozil in water. Shake to dissolve. Use this solution within 6 h.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 30-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution 1*

[Note—The relative retention times for cefprozil (*Z*)-isomer and cefprozil (*E*)-isomer are about 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.5 between cefprozil (*Z*)-isomer and cefprozil (*E*)-isomer, *System suitability solution*

Tailing factor: 0.9–1.1, *Standard solution 1*

Relative standard deviation: NMT 2.0%, *Standard solution 1*

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the amount (µg/mg) of cefprozil (*Z*)-isomer ($C_{18}H_{19}N_3O_5S$) in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak response of cefprozil (*Z*)-isomer from the *Sample solution*

r_S = peak response of cefprozil (*Z*)-isomer from *Standard solution 1*

C_S = concentration of USP Cefprozil (*Z*)-Isomer RS in *Standard solution 1* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil (*Z*)-Isomer RS (µg/mg)

Calculate the amount (µg/mg) of cefprozil (*E*)-isomer ($C_{18}H_{19}N_3O_5S$) in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak response of cefprozil (*E*)-isomer from the *Sample solution*

r_S = peak response of cefprozil (*E*)-isomer from *Standard solution 2*

C_S = concentration of USP Cefprozil (*E*)-Isomer RS in *Standard solution 2* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil (*E*)-Isomer RS (µg/mg)

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

Acceptance criteria: 900–1050 µg/mg on the anhydrous basis

IMPURITIES

• **Organic Impurities, Procedure 1**

Use *Organic Impurities, Procedure 1* when the impurity profile includes *Z*-cefprozil open ring, *E*-cefprozil open ring, and cefprozil related compound K.

Solution A: 11.5 g/L of monobasic ammonium phosphate in water. Adjust, if necessary, with phosphoric acid or ammonium hydroxide to a pH of 4.4.

Solution B: Acetonitrile and *Solution A* (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
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 gradient elution times in *Table 1* can be adjusted as necessary to achieve the separation described.]

Standard stock solution: 0.25 mg/mL each of USP Cefprozil (*Z*)-Isomer RS, USP Amoxicillin Related Compound I RS, and USP Cefprozil Related Compound D RS in a mixture of 1 M hydrochloric acid and *Solution A*. Prepare the solution as follows. Dissolve USP Amoxicillin Related Compound I RS, USP Cefprozil (*Z*)-Isomer RS, and USP Cefprozil Related Compound D RS in 1 M hydrochloric acid, using 20% of the final volume. Dilute with *Solution A* to volume.

Sensitivity solution: 2.5 µg/mL each of cefprozil (*Z*)-isomer, amoxicillin related compound I, and cefprozil related compound D in *Solution A* from *Standard stock solution*. Store the solution at 4°, and use within 8 h.

Standard solution: 50 µg/mL each of cefprozil (*Z*)-isomer, amoxicillin related compound I, and cefprozil related compound D in *Solution A* from the *Standard stock solution*. Store the solution at 4°, and use within 12 h.

Sample solution: 5 mg/mL of Cefprozil in a mixture of 1 M hydrochloric acid and *Solution A*, prepared as follows. Dissolve the Cefprozil first in 1 M hydrochloric acid using 4% of the final volume, and then dilute with *Solution A* to volume. Store the solution at 4°, and use within 3 h.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 4°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[NOTE—USP Cefprozil Related Compound D RS contains the (*Z*)- and (*E*)-isomers of cefprozil related compound D. See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.4 between the (*E*)-isomer of cefprozil related compound D and cefprozil (*Z*)-isomer, *Standard solution*

Relative standard deviation: NMT 10.0% for cefprozil, amoxicillin related compound I, and each isomer of cefprozil related compound D, *Standard solution*

Signal-to-noise ratio: NLT 10 for cefprozil, amoxicillin related compound I, and each isomer of cefprozil related compound D, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amoxicillin related compound I in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response of amoxicillin related compound I from the *Sample solution*

r_S = peak response of amoxicillin related compound I from the *Standard solution*

C_S = concentration of USP Amoxicillin Related Compound I RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of amoxicillin related compound I in USP Amoxicillin Related Compound I RS (mg/mg)

Calculate the percentage of cefprozil related compound D in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = sum of the responses for cefprozil related compound D (*Z*)-isomer and cefprozil related compound D (*E*)-isomer from the *Sample solution*

r_S = peak response of cefprozil related compound D (*Z*)-isomer from the *Standard solution*

C_S = concentration of USP Cefprozil Related Compound D RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of cefprozil related compound D (*Z*)-isomer in USP Cefprozil Related Compound D RS (mg/mg)

Calculate the percentage of each of the other impurities in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of cefprozil from the *Standard solution*

C_S = concentration of USP Cefprozil (*Z*)-Isomer RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil (*Z*)-Isomer RS (mg/mg)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amoxicillin related compound I[a]	0.40	0.3
Cefadroxil	0.54	0.5
Hydroxyphenyldiketopiperazine[b]	0.61	0.3
Cefprozil related compound D (*Z*)-isomer[c,d]	0.69	0.3
Cefprozil related compound D (*E*)-isomer[e]	0.91	
O-Acyl cefprozil[f]	0.76	0.2
Cefprozil (*Z*)-isomer	1.0	—
Cefprozil (*E*)-isomer	1.37	—
Z-Cefprozil open ring[g]	1.74	0.2
Cefprozil related compound H (*Z*)-isomer[h,i]	1.95	0.2
Cefprozil related compound H (*E*)-isomer[i]	2.19	
E-Cefprozil open ring[k]	2.08	0.2
Cefprozil related compound K[l,m]	2.76	0.1
	2.86	0.1
	2.91	0.1
	3.01	0.1
Any individual unspecified impurity	—	0.1
Total impurities	—	2.0

[a] (*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

[b] 3-(Aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

[c] 7-Amino-3-propenylcephalosporanic acid (*Z*-isomer); (6*R*,7*R*)-7-Amino-8-oxo-3-[(*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[d] The sum of the two isomers is reported. The limit for the sum is 0.3%.

[e] 7-Amino-3-propenylcephalosporanic acid (*E*-isomer); (6*R*,7*R*)-7-Amino-8-oxo-3-[(*E*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[f] (6*R*,7*R*)-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.

[g] (*R*)-2-{(*R*)-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5-[(*Z*)-prop-1-enyl]-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid.

[h] *N*-Acyl cefprozil (*Z*-isomer); (6*R*,7*R*)-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.

[i] The sum of the two isomers is reported. The limit for the sum is 0.2%.

[j] *N*-Acyl cefprozil (*E*-isomer); (6*R*,7*R*)-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.

[k] (*R*)-2-{(*R*)-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5-[(*E*)-prop-1-enyl]-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid.

[l] Hydroxyphenyldiketopiperazine lactone; 3-(5-Ethyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

[m] The system resolves four isomers of cefprozil related compound K.

• **Organic Impurities, Procedure 2**

Use *Organic Impurities, Procedure 2* when the impurity profile includes ethoxycarbonyl cefprozil, methoxycefadroxil, cefprozil delta-3 isomer, cefprozil amide, and cefprozil dimer.

Solution A: 4 g/L of monobasic sodium phosphate adjusted with dilute phosphoric acid (1 in 10) to a pH of 4.2 ± 0.05

Solution B: Acetonitrile and *Solution A* (1:1)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	70	30
40	40	60
50	0	100
60	0	100
62	95	5
70	95	5

Diluent: 0.85 g/L of monobasic potassium phosphate and 1.16 g/L of anhydrous dibasic sodium phosphate in water

System suitability stock solution: 0.15 mg/mL of USP Cefadroxil RS and 0.75 mg/mL of USP Cefprozil Related Compound D RS, prepared as follows. Dissolve USP Cefadroxil RS in *Solution A*, using 20% of the final volume. Add USP Cefprozil Related Compound D RS, mix, and dilute with *Diluent* to volume.

System suitability solution: 15 µg/mL of USP Cefadroxil RS and 75 µg/mL of USP Cefprozil Related Compound D RS from the *System suitability stock solution* and 1.5 mg/mL of USP Cefprozil RS in *Solution A*

Standard solution: 15 µg/mL of USP Cefprozil RS in *Solution A*

Sample solution: 1.5 mg/mL of Cefprozil in *Solution A*. Refrigerate the solution, and use within 1 h.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 4°

Column: NMT 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between the (*Z*)-isomer of cefprozil related compound D and cefadroxil; NLT 1.5 between cefadroxil and the (*E*)-isomer of cefprozil related compound D, *System suitability solution*

Relative standard deviation: NMT 5.0% for the sum of the cefprozil (*Z*)-isomer and cefprozil (*E*)-isomer, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = sum of the responses for cefprozil (*Z*)-isomer and cefprozil (*E*)-isomer from the *Standard solution*

C_S = concentration of USP Cefprozil RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil RS (mg/mg)

F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*. The reporting threshold is 0.05%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound I[a]	0.17	1.5	0.15
Cefprozil related compound D (*Z*)-isomer[b]	0.57	0.56	0.30
Cefadroxil	0.62	1.1	1.0
Methoxycefadroxil[c]	0.65	0.44	0.15
Cefprozil related compound D (*E*)-isomer[d]	0.73	0.56	0.30
Cefprozil delta-3 isomer[e]	0.92	0.95	0.2
Cefprozil (*Z*)-isomer	1.0	—	—
Cefprozil (*E*)-isomer	1.17	—	—
Cefprozil related compound H[f]	1.33	0.93	0.15
Cefprozil amide[g]	1.46	0.90	0.15
Ethoxycarbonylcefprozil[h]	2.08	0.70	0.15
Cefprozil dimer[i]	2.21	0.90	0.2
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	2.00

[a] (*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

[b] 7-Amino-3-propenylcephalosporanic acid (*Z*-isomer); (6*R*,7*R*)-7-Amino-8-oxo-3-[(*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[c] (6*R*,7*R*)-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.

[d] 7-Amino-3-propenylcephalosporanic acid (*E*-isomer); (6*R*,7*R*)-7-Amino-8-oxo-3-[(*E*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[e] (6*R*,7*R*)-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.

[f] *N*-Acyl cefprozil (*Z*-isomer); (6*R*,7*R*)-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.

[g] (*R*)-2-{(6*R*,7*R*)-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.

[h] (6*R*,7*R*)-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.

[i] (6*R*,7*R*)-7-[(*R*)-2-{(6*R*,7*R*)-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.

SPECIFIC TESTS

- **Crystallinity ⟨695⟩:** Meets the requirements
- **pH ⟨791⟩**

  Sample solution: 5 mg/mL in water

  Acceptance criteria: 3.5–6.5
- **Water Determination ⟨921⟩, *Method I*:** 3.5%–6.5%
- **Cefprozil (*E*)-Isomer Ratio**

  Buffer, Mobile phase, System suitability solution, Standard solution 1, Standard solution 2, Sample solution, Chromatographic system, and

  System suitability: Proceed as directed in the *Assay*.

  Analysis

  Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

  Calculate the ratio of the cefprozil (*E*)-isomer to total cefprozil in the portion of Cefprozil taken:

$$\text{Result} = E/(E + Z)$$

  E = amount of cefprozil (*E*)-isomer as determined in the *Assay* (µg/mg)

  Z = amount of cefprozil (*Z*)-isomer as determined in the *Assay* (µg/mg)

  Acceptance criteria: The ratio is 0.06–0.11.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, then the labeling states with which *Organic Impurities* test the article complies.
- **USP Reference Standards ⟨11⟩**

USP Amoxicillin Related Compound I RS
(*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.
$C_8H_9NO_3$ 167.16

USP Cefadroxil RS

USP Cefprozil RS

USP Cefprozil (*E*)-Isomer RS

USP Cefprozil (*Z*)-Isomer RS

USP Cefprozil Related Compound D RS
7-Amino-3-propenylcephalosporanic acid;
(6*R*,7*R*)-7-Amino-8-oxo-3-[(*Z*)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
$C_{10}H_{12}N_2O_3S$ 240.28

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CEFPROZIL	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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