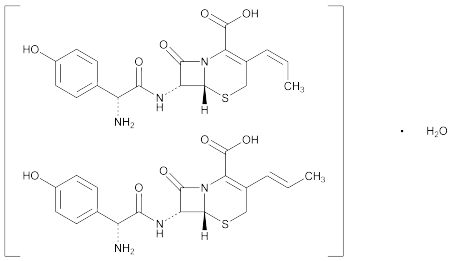
Cefprozil



$C_{18}H_{19}N_3O_5S \cdot H_2O$ 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 [121123-17-9].
Anhydrous 389.43
[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. Infrared Absorption** ⟨197K⟩
  Standard: ■USP Cefprozil RS■1S (*USP36*)
  Acceptance criteria: Meets the requirements
- **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

Change to read:

- **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) ■■1S (*USP36*)
  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;■1S (*USP36*) 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* ■■1S (*USP36*)
  Tailing factor: 0.9–1.1, *Standard solution 1* ■■1S (*USP36*)
  Relative standard deviation: NMT 2.0%, *Standard solution 1*
  Analysis
  Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*
  Calculate the amount (µg) of cefprozil (*Z*)-isomer ($C_{18}H_{19}N_3O_5S$) in each mg 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) of cefprozil (*E*)-isomer ($C_{18}H_{19}N_3O_5S$) in each mg 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 quantity, in µg, of cefprozil ($C_{18}H_{19}N_3O_5S$) in each mg 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

Add the following:

■• **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

Table 1 *(Continued)*

Time (min)	Solution A (%)	Solution B (%)
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 the table 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

Column: 40°

Autosampler: 4°

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.]

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	
Cefprozil related compound D (*E*)-isomer[e]	0.91	0.3
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	
Cefprozil related compound H (*E*)-isomer[j]	2.19	0.2
E-Cefprozil open ring[k]	2.08	0.2
	2.76	0.1
	2.86	0.1
	2.91	0.1
Cefprozil related compound K[l,m]	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.

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%.■1S (*USP36*)

Add the following:

■• **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
Column: NMT 30°
Autosampler: 4°
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● (RB 1-Oct-2013)
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● (RB 1-Oct-2013)
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● (RB 1-Oct-2013)

[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.

■1S (*USP36*)

SPECIFIC TESTS

- **CRYSTALLINITY** ⟨**695**⟩**:** Meets the requirements
- **pH** ⟨**791**⟩
  Sample solution: 5 mg/mL in water
  Acceptance criteria: 3.5–6.5
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** 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.

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  ■USP Amoxicillin Related Compound I RS
  (*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.
  $C_8H_9NO_3$ 167.16■1S (*USP36*)
  USP Cefadroxil RS
  ■USP Cefprozil RS■1S (*USP36*)
  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■1S (*USP36*)