Cefdinir for Oral Suspension

DEFINITION

Cefdinir for Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$). It may contain one or more suitable buffers, flavors, preservatives, stabilizing agents, sweeteners, and suspending agents.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: 10.7 mg/mL of anhydrous dibasic sodium phosphate and 3.4 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid or sodium hydroxide to a pH of 7.0 ± 0.05 before final dilution.

Solution A: 7 mg/mL of citric acid monohydrate. Adjust with phosphoric acid to a pH of 2.0 ± 0.05.

Mobile phase: Methanol, tetrahydrofuran, and *Solution A* (111:28:1000)

System suitability solution: 50 µg/mL of USP Cefdinir RS and 175 µg/mL of *m*-hydroxybenzoic acid in *Buffer*

Standard solution: 50 µg/mL of USP Cefdinir RS in *Buffer*

Sample solution: Equivalent to 50 µg/mL of cefdinir from constituted Cefdinir for Oral Suspension in *Buffer*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 15-cm; 4-µm packing L1
Flow rate: 1.4 mL/min
Injection volume: 15 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between cefdinir and *m*-hydroxybenzoic acid, *System suitability solution*
Tailing factor: NMT 2.0 for cefdinir, *System suitability solution*
Relative standard deviation: NMT 1.0% for cefdinir, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of cefdinir ($C_{14}H_{13}N_5O_5S_2$) in the portion of Cefdinir for Oral Suspension taken:

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

r_U = peak response of cefdinir from the *Sample solution*
r_S = peak response of cefdinir from the *Standard solution*
C_S = concentration of the *Standard solution* (µg/mL)
C_U = nominal concentration of cefdinir in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨**711**⟩

Medium: 0.05 M phosphate buffer, pH 6.8; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Detector: UV 290 nm
Standard solution: 0.14 mg/mL of USP Cefdinir RS in *Medium*
Sample solution: Transfer 5 mL, by weight, of the reconstituted Cefdinir for Oral Suspension into the vessel. After the appropriate time, withdraw a portion of the solution under test, and pass through a suitable filter of 0.45-µm pore size. Dilute a portion of each filtered sample with *Medium* as necessary to obtain a solution having a concentration of about 0.14 mg/mL of cefdinir.
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the percentage of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$) dissolved:

$$\text{Result} = (A_U/A_S) \times [(C_S \times d \times D \times V)/W \times L] \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
d = density of the Cefdinir for Oral Suspension (mg/mL)
D = dilution factor of the *Sample solution* (mL/mL)
V = volume of *Medium*, 900 mL
W = weight of Cefdinir for Oral Suspension taken (mg)
L = label claim (mg/mL)

Tolerances: NLT 80% (*Q*) of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meets the requirements for solids packaged in single-unit containers
- **DELIVERABLE VOLUME** ⟨**698**⟩**:** For solids packaged in single-unit containers, meets the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Solution A: 14.2 mg/mL of anhydrous dibasic sodium phosphate
Solution B: 13.6 mg/mL of monobasic potassium phosphate
Buffer: Combine appropriate amounts of *Solution A* and *Solution B* (about 2:1) to obtain a solution with a pH of 7.0 ± 0.1.
Solution C: Dilute tetramethylammonium hydroxide (10% aqueous) with water to obtain a 0.1% solution. Adjust with dilute phosphoric acid (1 in 10) to a pH of 5.5 ± 0.1.
Solution D: 37.2 mg/mL of edetate disodium
Solution E: To 1000 mL of *Solution C* add 0.4 mL of *Solution D*.
Solution F: Acetonitrile, methanol, *Solution C*, and *Solution D* (150: 100: 250: 0.2)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution E (%)	Solution F (%)
0	95	5
2	95	5
22	75	25

Table 1 *(Continued)*

Time (min)	Solution E (%)	Solution F (%)
32	50	50
37	50	50
38	95	5
58	95	5

System suitability stock solution 1: 40 µg/mL of USP Cefdinir Related Compound A RS in *Solution C*
System suitability stock solution 2: 40 µg/mL of USP Cefdinir Related Compound B RS in *Buffer*
System suitability solution: Transfer 37.5 mg of USP Cefdinir RS to a 25-mL volumetric flask, and add about 10 mL of *Buffer*. Add 5.0 mL each of *System suitability stock solution 1* and *System suitability stock solution 2*, and dilute with *Solution C* to volume.
Standard stock solution: 750 µg/mL of USP Cefdinir RS in *Buffer*
Standard solution: 15 µg/mL of USP Cefdinir RS from the *Standard stock solution* in *Solution C*
Sample solution: Transfer a quantity equivalent to 150 mg of cefdinir from the constituted Cefdinir for Oral Suspension to a 100-mL volumetric flask. Dissolve in 30 mL of *Buffer*, and dilute with *Solution C* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Column: 40°
Autosampler: 4°
Flow rate: 1 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between cefdinir and the third peak for USP Cefdinir Related Compound A RS, *System suitability solution*
Tailing factor: NMT 1.5 for cefdinir related compound B, *System suitability solution*
Relative standard deviation: NMT 2.0% for the cefdinir peak, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Cefdinir for Oral Suspension taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of cefdinir from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
C_U = nominal concentration of cefdinir in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 2*)
Acceptance criteria: See *Table 2*.

SPECIFIC TESTS

Change to read:

- **pH** ⟨**791**⟩**:** •3.2–4.8• (RB 1-Jun-2013)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **Labeling:** The label specifies the directions for the constitution of the powder and states the equivalent amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$) in a given volume of Cefdinir for Oral Suspension after constitution.
- **USP Reference Standards** ⟨**11**⟩
USP Cefdinir RS
USP Cefdinir Related Compound A RS
(2*R*)-2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid (three other stereoisomers are also present in this RS).
$C_{14}H_{15}N_5O_6S_2$ 413.43
USP Cefdinir Related Compound B RS
(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0)]oct-2-ene-2-carboxylic acid.
$C_{14}H_{13}N_4O_4S_2$ 365.41

Table 2

Name	Relative Retention Time	Relative Response Factor	Reporting Threshold (% Cefdinir)	Acceptance Criteria, NMT (%)
Thiazolylacetyl glycine oxime[a]	0.10	1.1	0.1	0.5
Thiazolylacetyl glycine oxime acetal[b]	0.13	1.1	0.1	0.6
Cefdinir sulfoxide[c]	0.36	1.0	0.05	0.2
Cefdinir thiazine analog[d]	0.46	1.5	0.05	0.3
3-Methyl cefdinir[e]	0.75	1.0	0.05	0.7
Cefdinir impurity 1[f]	0.77	1.0	0.05	0.2
Cefdinir related compound A (cefdinir open ring lactone a)[g,h]	0.85	1.5	0.1	3.3
Cefdinir related compound A (cefdinir open ring lactone b)[g,h]	0.94	1.5	0.1	
Cefdinir related compound A (cefdinir open ring lactone c)[g,h]	1.11	1.5	0.1	
Cefdinir related compound A (cefdinir open ring lactone d)[g,h]	1.14	1.5	0.1	
7S-Cefdinir[i]	1.18	1.1	0.05	0.2
Cefdinir lactone[j]	1.23	1.2	0.05	0.8
Cefdinir related compound B[k]	1.28	1.1	0.05	0.2
Cefdinir isoxazole analog[l]	1.37	1.4	0.05	0.5
Cefdinir impurity 2[f]	1.44	1.0	0.05	0.2
Cefdinir glyoxalic analog[m]	1.49	1.0	0.05	0.2
E-Cefdinir[n]	1.51	1.1	0.05	1.2
Cefdinir decarboxy open ring lactone a[o,p]	1.62	1.3	0.05	1.1
Cefdinir decarboxy open ring lactone b[o,p]	1.64	1.3	0.05	
Cefdinir impurity 3[f]	1.82	1.0	0.05	0.2
Individual unidentified impurities	—	1.0	0.05	0.2
Total impurities	—	—	—	6.2

[a] *N*-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetyl]glycine.
[b] (*Z*)-2-(2-Aminothiazol-4-yl)-*N*-(2,2-dihydroxyethyl)-2-(hydroxyimino)acetamide.
[c] (6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-5,8-dioxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[d] (*R*,*Z*)-2-{(*R*)-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido](carboxy)methyl}-5-ethylidene-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid.
[e] (6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[f] Cefdinir impurity 1, cefdinir impurity 2, and cefdinir impurity 3 are unidentified impurities.
[g] Cefdinir related compound A is a mixture of four isomers labeled cefdinir open ring lactones a, b, c, and d. The sum of the values is reported; the limit for the sum of the four isomers is 3.3%.
[h] 2(*R*)-2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid.
[i] (6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[j] (*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-((3*RS*,5a*R*,6*R*)-3-methyl-1,7-dioxo-1,3,4,5*a*,6,7-hexahydroazeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl)acetamide.
[k] (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[l] (6*R*,7*R*)-7-(4-Hydroxyisoxazole-3-carboxamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[m] (6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-oxoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[n] (6*R*,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[o] Cefdinir decarboxy open ring lactone is a mixture of two isomers labeled cefdinir decarboxy open ring lactone a and b. The sum of the values is reported; the limit for the sum of the two isomers is 1.1%.
[p] (*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-{[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]methyl}acetamide.