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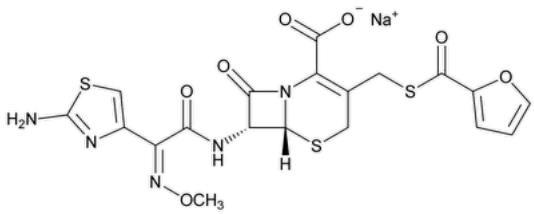
Ceftiofur Sodium



$C_{19}H_{16}N_5NaO_7S_3$ 545.54
$C_{19}H_{16}N_5NaO_7S_3 \cdot H_2O$ 563.55
$C_{19}H_{16}N_5NaO_7S_3 \cdot 3H_2O$ 599.59

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-, monosodium salt, [6*R*-[6α,7β(*Z*)]]-;
Sodium (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(*Z*)-(*O*-methyloxime), 2-furoate (ester) CAS RN®: 104010-37-9.

DEFINITION

Ceftiofur Sodium is the sodium salt of ceftiofur. It is anhydrous or contains one or three molecules of water of hydration. It has a potency equivalent to NLT 862 µg/mg and NMT 970 µg/mg of ceftiofur ($C_{19}H_{17}N_5O_7S_3$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

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

• **B.** 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**

Solution A: Tetrabutylammonium hydroxide, 40% in water

Solution B: Dissolve 3.85 g of ammonium acetate and 13.5 mL of *Solution A* in 700 mL of water. Adjust with glacial acetic acid to a pH of 6.7.

Mobile phase: Mix 700 mL of *Solution B* with 200 mL of methanol and 110 mL of tetrahydrofuran.

Diluent: 0.05 M ammonium acetate

Standard solution: 0.16 mg/mL of USP Ceftiofur Sodium Trihydrate RS in *Diluent*

Sample solution: 0.16 mg/mL of Ceftiofur Sodium in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in µg/mg, of ceftiofur ($C_{19}H_{17}N_5O_7S_3$) in the portion of Ceftiofur Sodium taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = concentration of Ceftiofur Sodium in the *Sample solution*, corrected for water (mg/mL)

P = potency of ceftiofur in USP Ceftiofur Sodium Trihydrate RS (µg/mg)

Acceptance criteria: 862–970 µg/mg on the anhydrous and solvent-free basis

IMPURITIES

• **Low Molecular Weight Impurities**

Solution A: Water and trifluoroacetic acid (1000:1)

Solution B: Acetonitrile and trifluoroacetic acid (1000:1)

Solution C: *Solution A* and *Solution B* (950:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	0	100
15	18	82
50	18	82
110	60	40
111	0	100
120	0	100

Buffer: 3.5 g/L of sodium phosphate dibasic dihydrate, adjusted with phosphoric acid to a pH of 8.0

Diluent: Acetonitrile and *Buffer* (40:60)

System suitability solution: 1 mg/mL of USP Ceftiofur System Suitability Mixture RS in *Diluent*. Sonicate as needed to dissolve.

Peak identification solution: 15 µg/mL of USP Cefotaxime Sodium RS in *Diluent*

Standard solution: 0.005 mg/mL of USP Ceftiofur Sodium Trihydrate RS in *Diluent*

Sample solution: 1 mg/mL of Ceftiofur Sodium in *Diluent*. Inject within 20 min of preparation.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: 3.5 times the retention time of ceftiofur

System suitability

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

[Note—The relative retention times for ceftiofur delta-3 isomer and ceftiofur are 0.93 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between ceftiofur delta-3 isomer and ceftiofur, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis

Samples: *Sample solution* and *Peak identification solution*

[Note—The elution order of the *N*-deacyl ceftiofur and cefotaxime peaks may be reversed depending on the column used. Determine the location of the cefotaxime peak by using the *Peak identification solution*.]

Calculate the percentage of each impurity in the portion of Ceftiofur Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (F_1/F_2) \times 100$$

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

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

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

C_U = concentration of Ceftiofur Sodium in the *Sample solution*, corrected for water (mg/mL)

P = potency of ceftiofur in USP Ceftiofur Sodium Trihydrate RS (µg/mg)

F_1 = conversion factor, 0.001 mg/µg

F_2 = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Aminothiazolyl oxime[a]	0.07	1.5	0.5
2-Furoic acid[b]	0.21	2.4	0.5
Thiofuroic acid[c]	0.30	0.5	0.5
Ceftiofur thiolactone[d]	0.43	1.0	0.5
N-Deacyl ceftiofur[e]	0.45	1.0	0.5
Cefotaxime (if present)[f,g]	0.47	1.0	0.5
Ceftiofur mercaptan[h]	0.52	1.0	0.5
Ceftiofur disulfide dimer[i]	0.85	0.75	0.5
Ceftiofur delta-3 isomer[j]	0.93	1.0	0.5
Ceftiofur	1.0	—	—
Ceftiofur *E*-isomer[k]	1.4	1.0	0.5
Ceftiofur dioxime[l]	2.1	1.0	0.5
N-Furoyl ceftiofur (if present)[g,m]	2.3	1.0	0.5
Difuroyl disulfide[n]	2.4	1.0	0.5
Any other individual impurity	—	1.0	0.5
Total impurities	—	—	2.2

[a] (*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetic acid.

[b] Furan-2-carboxylic acid.

[c] Furan-2-carbothioic acid.

[d] (*Z*)-2-(2-Aminothiazol-4-yl)-*N*-((5a*R*,6*R*)-1,7-dioxo-1,3,4,5a,6,7-hexahydroazeto[2,1-b]thieno[3,4-*d*][1,3]thiazin-6-yl)-2-(methoxyimino)acetamide.

[e] (6*R*,7*R*)-7-Amino-3-((furan-2-carbonylthio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[f] (6*R*,7*R*)-3-(Acetoxymethyl)-7-((*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[g] If possible from the manufacturing process.

[h] (6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-(mercaptomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[i] (6*R*,6'*R*,7*R*,7'*R*,*Z*)-3,3'-[Dithiobis(methylene)]bis{7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid}.

[j] (6*R*,7*R*)-7-((*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((furan-2-carbonylthio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

[k] (6*R*,7*R*)-7-((*E*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((furan-2-carbonylthio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[l] (6*R*,7*R*)-7-{(*Z*)-2-(2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]thiazol-4-yl)-2-(methoxyimino)acetamido}-3-{[(furan-2-carbonyl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[m] (6*R*,7*R*)-3-{[(Furan-2-carbonyl)thio]methyl}-7-{(*Z*)-2-[2-(furan-2-carboxamido)thiazol-4-yl]-2-(methoxyimino)acetamido}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[n] Difuran-2-oyl disulfide.

Change to read:

• High Molecular Weight Impurities (Ceftiofur Polymers)

[Note—Perform this test if this impurity is possible from the manufacturing process.]

To minimize leaching of plastic components, avoid contact between the *Mobile phase* and plastics during all steps including during preparation of the *Mobile phase*, the *System suitability solution*, and the *Sample solution*, and when filling the injection vial.

Solution A: 0.68 g/L of monobasic potassium phosphate. Adjust with 45% potassium hydroxide solution to a pH of 7.5.

Mobile phase: 10 g/L of electrophoresis grade sodium dodecyl sulfate in *Solution A*. Stir or slightly heat to dissolve.

Blank: Use the *Mobile phase*.

System suitability solution: 0.15 mg/mL each of USP Ceftiofur System Suitability Mixture RS in *Mobile phase*. Sonicate if necessary to dissolve. Inject within 20 min of preparation.

Sample solution: 0.15 mg/mL of Ceftiofur Sodium in *Mobile phase*. Inject within 20 min of preparation.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.0-mm × 25-cm; 5-µm packing L20

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of the ceftiofur peak

System suitability

Sample: *System suitability solution*

[Note—Adjust the chromatographic system so that the retention time of ceftiofur is NLT 2.5 min. The relative retention times of ceftiofur *E*-isomer and ceftiofur are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.0 between ceftiofur and ceftiofur *E*-isomer

Analysis

Samples: *Blank* and *Sample solution*

Calculate the percentage of high molecular weight impurities in the portion of Ceftiofur Sodium taken:

$$\text{Result} = \{100 \times (r_U/F)/[(r_U/F) + r_C + r_A]\} - T$$

r_U = sum of the responses of all peaks that elute prior to ceftiofur from the *Sample solution*, corrected for the *Blank* if necessary

F = relative response factor, 0.8

r_C = peak response of ceftiofur from the *Sample solution*▲▲ (ERR 1-Jun-2019)

r_A = sum of the responses of all peaks that elute after ceftiofur from the *Sample solution*▲▲ (ERR 1-Jun-2019)

T = total impurities from *Table 2*

Acceptance criteria

Total high molecular weight impurities: NMT 11.0%

• **Residual Solvents** ⟨467⟩

Acceptance criteria

Tetrahydrofuran (if present): NMT 0.7%

Acetone (if present): NMT 3.5%

[Note—For the *Acceptance criteria* for any other residual solvents, see *Residual Solvents* ⟨467⟩.]

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 50 mg/mL

Acceptance criteria: 5.0–7.5

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 10 mg/mL in water

Acceptance criteria: −60.0° to −74.0°

• **Bacterial Endotoxins Test** ⟨85⟩**:** Where the label states that Ceftiofur Sodium is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 1.0 USP Endotoxin Unit/mg of ceftiofur sodium.

• **Water Determination** ⟨921⟩, *Method I*

Acceptance criteria

Where it is labeled as anhydrous: NMT 2.0%

Where it is labeled as the monohydrate: NMT 4.0%

Where it is labeled as the trihydrate: NMT 10.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature except where it is labeled as monohydrate, in which case it should be stored in the freezer.

• **Labeling:** Label it to indicate that it is intended for veterinary use only and to indicate whether it is anhydrous, monohydrate, or trihydrate. Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference Standards** ⟨11⟩

USP Cefotaxime Sodium RS

USP Ceftiofur Sodium Trihydrate RS

USP Ceftiofur System Suitability Mixture RS

This is a mixture of ceftiofur, ceftiofur delta-3 isomer, ceftiofur *E*-isomer, and other impurities.

Ceftiofur delta-3 isomer

(6*R*,7*R*)-7-((*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((furan-2-carbonylthio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

$C_{19}H_{17}N_5O_7S_3$ 523.56

Ceftiofur *E*-isomer

(6*R*,7*R*)-7-((*E*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((furan-2-carbonylthio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{19}H_{17}N_5O_7S_3$ 523.56

USP Endotoxin RS

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

Topic/Question	Contact	Expert Committee
CEFTIOFUR SODIUM	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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