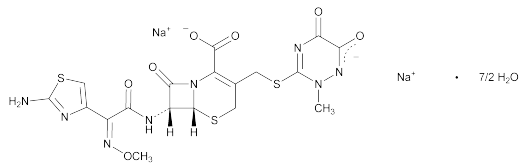
Ceftriaxone Sodium



$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3^1/_2H_2O$ 661.60
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6*R*-[6α,7β(*Z*)]]-, hydrate, (2:7);
(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(*O*-methyloxime), disodium salt, hemiseptahydrate [104376-79-6].
Anhydrous 598.56

DEFINITION

Ceftriaxone Sodium contains the equivalent of NLT 795 µg/mg of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL** ⟨191⟩, *Sodium*

ASSAY

Change to read:

- **PROCEDURE**

•Protect solutions containing ceftriaxone sodium from light.• (IRA 1-Aug-2016)

Solution A: 9 g/L of monobasic potassium phosphate in water

Solution B: 24 g/L of dibasic sodium phosphate, dodecahydrate in water

Solution C: 20 g/L of citric acid in water. Adjust with 10 N sodium hydroxide to a pH of 5.0 prior to final dilution.

Buffer: Combine 389 mL of *Solution A* and 611 mL of *Solution B*. Adjust with 10 N sodium hydroxide TS or phosphoric acid to a pH of 7.0.

Mobile phase: Dissolve 2.0 g each of tetradecylammonium bromide and tetraheptylammonium bromide in a mixture of 440 mL of water, 55 mL of *Buffer*, 5.0 mL of *Solution C*, and 500 mL of acetonitrile.

System suitability solution: 50 µg/mL of USP Ceftriaxone Sodium RS and 50 µg/mL of USP Ceftriaxone Sodium *E*-Isomer RS in *Mobile phase*

Standard solution: 0.3 mg/mL of USP Ceftriaxone Sodium RS in *Mobile phase*

Sample solution: 0.3 mg/mL of Ceftriaxone Sodium in *Mobile phase*

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: 1.5 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for ceftriaxone and ceftriaxone *E*-isomer are 1.0 and 1.4, respectively.]
Suitability requirements
Resolution: NLT 3.0 between the ceftriaxone and ceftriaxone *E*-isomer peaks, *System suitability solution*
Tailing factor: NMT 2, *Standard solution*
Relative standard deviation: NMT 0.7%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the quantity, in µg/mg, of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$) in the portion of Ceftriaxone Sodium taken:

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

r_U = peak response of ceftriaxone from the *Sample solution*
r_S = peak response of ceftriaxone from the *Standard solution*
C_S = concentration of USP Ceftriaxone Sodium RS in the *Standard solution* (mg/mL)
C_U = concentration of Ceftriaxone Sodium in the *Sample solution* (mg/mL)
P = potency of ceftriaxone in USP Ceftriaxone Sodium RS (µg/mg)

Acceptance criteria: NLT 795 µg/mg on the anhydrous basis

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

•Protect solutions containing ceftriaxone sodium from light.• (IRA 1-Aug-2016)

Solution A, Solution B, Solution C, Buffer, Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 3 µg/mL of USP Ceftriaxone Sodium RS in *Mobile phase*

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for ceftriaxone and ceftriaxone *E*-isomer are listed in *Table 1*.]
Suitability requirements
Resolution: NLT 3.0 between the ceftriaxone *E*-isomer and ceftriaxone peaks, *System suitability solution*
Signal-to-noise ratio: NLT 10, *Standard solution*

Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of each individual impurity in the portion of Ceftriaxone Sodium taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of ceftriaxone from the *Standard solution*

C_S = concentration of USP Ceftriaxone Sodium RS in the *Standard solution* (mg/mL)
C_U = concentration of Ceftriaxone Sodium in the *Sample solution* (mg/mL)
P = potency of ceftriaxone in USP Ceftriaxone Sodium RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 1*. Disregard any peak below 0.1%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Deacetylcefotaxime lactone[a]	0.20	0.5
7-Aminocephalosporanic acid[b,c] (if present)	0.34	0.5
Ceftriaxone triazine analog[d]	0.62	1.0
Ceftriaxone benzothiazolyloxime[e]	0.72	0.2
Deacyl ceftriaxone[f]	0.78	0.5
Ceftriaxone	1.0	—
Ceftriaxone 3-ene isomer[g]	1.3	0.3
Ceftriaxone *E*-isomer[h]	1.4	0.5
Any individual unspecified impurity	—	0.2
Total impurities	—	2.5

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

[b] 7-ACA; (6*R*,7*R*)-3-(Acetoxymethyl)-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

[c] To be reported if present in the impurity profile.

[d] 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione.

[e] (*Z*)-*S*-Benzothiazol-2-yl 2-(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate.

[f] (6*R*,7*R*)-7-Amino-3-{[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

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

[h] (6*R*,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-{[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

SPECIFIC TESTS

- **Crystallinity ⟨695⟩:** Meets the requirements
- **pH ⟨791⟩**
  Sample solution: 100 mg/mL
  Acceptance criteria: 6.0–8.0
- **Water Determination ⟨921⟩,** *Method I***:** 8.0%–11.0%
- **Sterility Tests ⟨71⟩,** *Test for Sterility of the Product to Be Examined***,** *Membrane Filtration***:** Where the label states that it is sterile, it meets the requirements.
- **Bacterial Endotoxins Test ⟨85⟩:** Where the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.20 USP Endotoxin Units/mg of ceftriaxone.

ADDITIONAL REQUIREMENTS

Change to read:

- **Packaging and Storage:** Preserve in tight containers, protected from light. (IRA 1-Aug-2016)
- **Labeling:** 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 Ceftriaxone Sodium RS
  USP Ceftriaxone Sodium *E*-Isomer RS
  (6*R*,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-{[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, disodium salt.
  $C_{18}H_{16}N_8Na_2O_7S_3$ 598.53
  USP Endotoxin RS