Ceftriaxone for Injection

DEFINITION

Ceftriaxone for Injection contains an amount of Ceftriaxone Sodium equivalent to NLT 776 µg/mg of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$), calculated on the anhydrous basis, and the equivalent of NLT 90.0% and NMT 115.0% of the labeled amount of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$).

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*.

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 TS to a pH of 5.0 prior to 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 each of USP Ceftriaxone Sodium RS and 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 1: Nominally 0.3 mg/mL of ceftriaxone from Ceftriaxone for Injection in *Mobile phase*

Sample solution 2 (where it is represented as being in a single-dose container)**:** Nominally 0.3 mg/mL of ceftriaxone in *Mobile phase* prepared as follows. Constitute Ceftriaxone for Injection in a volume of water corresponding to the volume of solvent specified in the labeling. Withdraw all of the withdrawable contents using a suitable hypodermic needle and syringe, and transfer to a suitable volumetric flask. Dilute with *Mobile phase* to volume.

Sample solution 3 (where the label states the quantity of ceftriaxone in a given volume of constituted solution)**:** Nominally 0.3 mg/mL of ceftriaxone in *Mobile phase* prepared as follows. Constitute Ceftriaxone for Injection in a volume of water corresponding to the volume of solvent specified in the labeling, and dilute with *Mobile phase* to final volume.

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*, •*Sample solution 1*, and *Sample solution 2* or *Sample solution 3*• (IRA 1-Aug-2016)
Calculate the quantity, in µg/mg, of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$) in the portion of Ceftriaxone for Injection taken:

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

r_U = peak response of ceftriaxone from *Sample solution 1*
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 = nominal concentration of ceftriaxone in *Sample solution 1* (mg/mL)
P = potency of ceftriaxone in USP Ceftriaxone Sodium RS (µg/mg)

Acceptance criteria: NLT 776 µg/mg on the anhydrous basis

Calculate the percentage of the labeled amount of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$) in the portion of Ceftriaxone for Injection withdrawn from the container or in the portion of the constituted solution:

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

r_U = peak response of ceftriaxone from *Sample solution 2* or *Sample solution 3*
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 = nominal concentration of ceftriaxone in *Sample solution 2* or *Sample solution 3* (mg/mL)
P = potency of ceftriaxone in USP Ceftriaxone Sodium RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–115.0% of the labeled amount of ceftriaxone

PERFORMANCE TESTS

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meets the requirements

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, •• (IRA 1-Aug-2016) and **Chromatographic system:** Proceed as directed in the *Assay*.

•**Standard solution:** 3 µg/mL of USP Ceftriaxone Sodium RS in *Mobile phase*• (IRA 1-Aug-2016)

Sample solution: Nominally 0.3 mg/mL of ceftriaxone from Ceftriaxone for Injection in *Mobile phase*

System suitability
Sample: *System suitability 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 and ceftriaxone *E*-isomer
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Ceftriaxone for Injection 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 = nominal concentration of ceftriaxone 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]	0.34	—● (IRA 1-Aug-2016)
Ceftriaxone triazine analog[c]	0.62	1.0
Ceftriaxone benzothiazolyl oxime[d]	0.72	0.2
Deacyl ceftriaxone[e]	0.78	1.0

[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] Process impurities that are controlled in the drug substance are not to be reported, are not included in total impurities, and are listed here for information only.● (IRA 1-Aug-2016)
[c] 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione.
[d] (*Z*)-*S*-Benzothiazol-2-yl 2-(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate.
[e] (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.
[f] (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● (IRA 1-Aug-2016)-ene-2-carboxylic acid.
[g] (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.

Table 1 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ceftriaxone	1.0	—
Ceftriaxone-3-ene isomer[f]	1.3	0.3
Ceftriaxone *E*-isomer[g]	1.4	1.0
Any individual unspecified impurity	—	0.2
Total impurities	—	●5.0● (IRA 1-Aug-2016)

[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] Process impurities that are controlled in the drug substance are not to be reported, are not included in total impurities, and are listed here for information only.● (IRA 1-Aug-2016)
[c] 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione.
[d] (*Z*)-*S*-Benzothiazol-2-yl 2-(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate.
[e] (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.
[f] (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● (IRA 1-Aug-2016)-ene-2-carboxylic acid.
[g] (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

Change to read:

- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements for ●*Injections and Implanted Drug Products* ⟨1⟩*, Product Quality Tests Common to Parenteral Dosage Forms, Specific Tests, Completeness and clarity of solutions*.● (CN 1-May-2016)
- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** NMT 0.20 USP Endotoxin Units/mg of ceftriaxone
- **STERILITY TESTS ⟨71⟩,** *Test for Sterility of the Product to Be Examined, Membrane Filtration*: It meets the requirements.
- **PARTICULATE MATTER IN INJECTIONS ⟨788⟩:** Meets the requirements for small-volume injections
- **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%

Change to read:

- **OTHER REQUIREMENTS:** It meets the requirements for ●*Labeling* ⟨7⟩*, Labels and Labeling for Injectable Products*.● (CN 1-May-2016)

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** •Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging, Sterile solids packaging,*• (CN 1-May-2016) •and protected from light.• (IRA 1-Aug-2016)

• **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