Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2021
Document Type: USP Monographs
DocId: GUID-B4D6DBD6-A660-4A63-847A-EA39A1EBAA63_4_en-US
DOI: https://doi.org/10.31003/USPNF_M13987_04_01
DOI Ref: 4b9pa

Cefepime for Injection

DEFINITION

Cefepime for Injection is a sterile mixture of Cefepime Hydrochloride and Arginine. It contains the equivalent of NLT 90.0% and NMT 115.0% of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$).

IDENTIFICATION

• **A. Thin-Layer Chromatographic Identification Test ⟨201⟩**

Standard solution: 20 mg/mL of arginine

Sample solution: 40 mg/mL of Cefepime for Injection

Developing solvent system: *n*-Propyl alcohol, ammonium hydroxide, and water (7:4:5)

Analysis

Samples: *Standard solution* and *Sample solution*

Proceed as directed in ⟨201⟩, except to spray the plate with ninhydrin TS.

Acceptance criteria: Arginine appears as a dark red spot. The intensity and the R_F value of the spot from the *Sample solution* correspond to those from the *Standard solution*.

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

Add the following:

▲• **C.** The UV spectrum of the cefepime peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲

(USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

Solution A: 0.68 mg/mL of monobasic potassium phosphate in water

Solution B: Acetonitrile and *Solution A* (1:9), adjusted with 2% phosphoric acid or 2% potassium hydroxide to a pH of 5.0

Solution C: Acetonitrile and *Solution A* (1:1), adjusted with 2% phosphoric acid or 2% potassium hydroxide to a pH of 5.0

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
10	100	0
30	50	50
35	50	50
36	100	0
45	100	0

Standard solution: 1.4 mg/mL of USP Cefepime Hydrochloride RS in *Solution B*. ▲Sonicate if necessary. Store this solution in a refrigerator and use within 12 h.▲ (USP 1-May-2021)

Sample solution: Constitute one container of Cefepime for Injection as directed on the label, and dilute using *Solution B* to 1 mg/mL of cefepime. [Note—For products that are designed for administration with a syringe, withdraw the entire withdrawable contents of the vial and transfer to a suitable volumetric flask. Dilute with *Solution B* to volume. For all other types, transfer the contents of the reconstituted vial quantitatively to a suitable volumetric flask, and dilute with *Solution B* to volume.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. ▲For *Identification C*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2021)

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲the labeled amount of cefepime▲ (USP 1-May-2021) ($C_{19}H_{24}N_6O_5S_2$) in the portion of Cefepime for Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \blacktriangle \times P \times F \blacktriangle_{\text{(USP 1-May-2021)}} \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Cefepime Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of cefepime in the *Sample solution* (mg/mL)

▲P = potency of cefepime in USP Cefepime Hydrochloride RS (µg/mg)

F = conversion factor, 0.001 mg/µg▲ (USP 1-May-2021)

Acceptance criteria: 90.0%–115.0%

PERFORMANCE TESTS

• **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements

IMPURITIES

Change to read:

• ▲▲ (USP 1-May-2021) **Limit of *N*-Methylpyrrolidine**

Mobile phase: Acetonitrile and 0.01 N nitric acid (1:19)

Standard solution: 0.05 mg/mL of *N*-methylpyrrolidine in 0.002 N nitric acid

Sample solution: Equivalent to 5 mg/mL of cefepime hydrochloride in 0.002 N nitric acid.

[Note—Inject this solution immediately.]

Chromatographic system

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

Mode: LC

Detector: Conductivity

Column: 4.0-mm x 25-cm; 5-µm packing L76

Flow rate: 1 mL/min

Injection volume: 10 µL

▲**Run time:** About 6 times the retention time of the *N*-methylpyrrolidine peak from the *Sample solution*▲ (USP 1-May-2021)

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 4.0%

Analysis

Samples: *Standard solution* and *Sample solution*▲▲ (USP 1-May-2021)

Calculate the percentage of *N*-methylpyrrolidine in the portion of Cefepime for Injection taken:

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

r_U = peak response of *N*-methylpyrrolidine from the *Sample solution*

r_S = peak response of *N*-methylpyrrolidine from the *Standard solution*

C_S = concentration of *N*-methylpyrrolidine in the *Standard solution* (mg/mL)

C_U = nominal concentration of cefepime in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 1.0%

Change to read:

• ▲▲ (USP 1-MAY-2021) **OTHER ORGANIC IMPURITIES**

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

System suitability solution: 1.4 mg/mL of USP Cefepime Hydrochloride RS and 15 µg/mL each of USP Cefepime Related Compound D RS and USP Cefepime Related Compound E RS in *Solution B*

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between cefepime related compound E and cefepime related compound D

Tailing factor: NMT 1.5 for cefepime

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Cefepime for Injection taken:

$$\text{Result} = (r_U/r_T) \times 1/F \times 100$$

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

r_T = sum of relevant peak responses from the *Sample solution*

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

Acceptance criteria: See *Table 2*. [NOTE—The reporting level is 0.2% for cefepime impurity C and 0.05% for all other related compounds.]▲▲ (USP 1-May-2021)

Table 2

Name	Relative Retention Time ▲▲ (USP 1-May-2021)	Relative Response Factor	Acceptance Criteria, NMT (%)
Cefepime amine derivative[a] ▲▲ (USP 1-May-2021) (cefepime related compound E)	0.4	—	—
Thiazolylglyoxalic methyloxime[a] (cefepime related compound D)	0.5	—	—
Thiazolyloxime acetaldehyde[b]	0.6	0.63	0.5
Cefepime dimer[a,c] (cefepime related compound F)	0.8	—	—
Cefepime	1.0	—	—
E-Cefepime[d] (cefepime related compound A)	2.7	0.71	0.5
Cefepime dioxime[a,e] (cefepime related compound B)	4.3	—	—
Any individual unspecified impurity	—	1.0	0.5

Name	Relative Retention Time ▲▲ (USP 1-May-2021)	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities▲[f]▲ (USP 1-May-2021)	—	—	2.2

[a] These impurities are synthetic process impurities that are controlled in the drug substance. They are listed here for reference only.

[b] (Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)-N-(2-oxoethyl)acetamide. (cefepime related compound C)

[c] 1-{[(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2-{(6*R*,7*R*)-2-carboxy-3-[(1-methylpyrrolidinium-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-ylcarbamoyl}-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-3-yl]methyl}-1-methylpyrrolidinium chloride.

[d] 1-({(6*R*,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl}methyl)-1-methylpyrrolidinium chloride.

[e] 1-({(6*R*,7*R*)-7-[(*Z*)-2-{2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxy imino)acetamido]thiazol-4-yl}-2-(methoxyimino)acetamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl}methyl)-1-methylpyrrolidinium chloride.

[f] Total impurities include *N*-methylpyrrolidine.

SPECIFIC TESTS

• **Injections and Implanted Drug Products ⟨1⟩, *Product Quality Tests Common to Parenteral Dosage Forms, Specific Tests, Completeness and Clarity of Solutions*:** At the time of use, it meets the requirements.

Change to read:

• **Bacterial Endotoxins Test ⟨85⟩:** ▲Meets the requirements▲ (USP 1-May-2021)

Change to read:

• **Sterility Tests ⟨71⟩:** Meets the requirements ▲▲ (USP 1-May-2021)

• **pH ⟨791⟩**

Sample solution: 100 mg/mL of cefepime

Acceptance criteria: 4.0–6.0

Delete the following:

▲• **Water Determination ⟨921⟩, *Method I*:** NMT 4.0% ▲ (USP 1-May-2021)

• **Other Requirements:** Meets the requirements for *Labeling ⟨7⟩, Labels and Labeling for Injectable Products*

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in tight, light-resistant containers as described under *Packaging and Storage Requirements ⟨659⟩*.▲▲ (USP 1-May-2021) and store in a refrigerator or at controlled room temperature. Store reconstituted solution in a refrigerator for NMT 7 days.

• **Labeling:** Label it to indicate that it is to be diluted with a suitable parenteral vehicle before intravenous infusion.

• **USP Reference Standards ⟨11⟩**

USP Cefepime Hydrochloride RS

USP Cefepime Related Compound D RS

Thiazolylglyoxalic methyloxime;
(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetic acid.
$C_6H_7N_3O_3S$ 201.20

USP Cefepime Related Compound E RS

Cefepime amine derivative;
1-{[(6*R*,7*R*)-7-Amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl}-1-methylpyrrolidin-1-ium chloride.
$C_{13}H_{20}ClN_3O_3S$ 333.83

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 44(2)
Current DocID: GUID-B4D6DBD6-A660-4A63-847A-EA39A1EBAA63_4_en-US
DOI: https://doi.org/10.31003/USPNF_M13987_04_01
DOI ref: 4b9pa