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NOOTAN PHARMACEUTICALS, BAROTIWALA, BADDI

STANDARD TEST SPECIFICATION QUALITY CONTROL DEPARTMENT			
RAW MATERIAL SPECIFICATION			
Name of Material	CEFEPIME FOR INJECTION USP		
Reference	USP	Spec/STP No.	RMS/033
Supersedes	00	Revision No.	01
Effective Date	02/03/2023	Review Date	01/03/2025

Sr. No.	Tests	Specification
1.	Description	White to Pale yellow Powder.
2.	Solubility	Freely Soluble in water.
3.	Identification: A) By TLC B) By HPLC	Arginine appears as a dark red spot. The intensity and the RF value of the spot from the Sample solution correspond to those from the Standard Solution. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
4.	Assay	Between 90.00% to 115.0%
5.	Uniformity of Dosage Units	Meets the requirements
6.	Organic Impurities	NMT 1.0%
7.	Injection & Implanted Drug Product	Meets the requirements
8.	Bacterial Endotoxins Test	NMT 0.06
9.	Sterility Test	Meets the requirements
10.	pH	Between 4.0-6.0
11.	Water Determination	NMT 4.0%

	Prepared by	Checked by	Reviewed by	Approved by
Department	QC	QC	QA	QA
Sign.	R	M		dk
Date	02/03/2023	02/03/2023	02/03/2023	02/03/2023
Name	Reena	Meenakshi Bhatt	Jyotish Kumar	Deeksha

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1.0 DESCRIPTION :

Take 1.0 gm of the sample in a petri dish and observe the colour and check visually for the presence of any foreign particles in the samples.

Observation: White to Pale yellow Powder.

2.0 Solubility: Freely Soluble in water.

Descriptive Term	Volume of solvent in ml/gm of sample
Very Soluble	Less than 1.0 ml
Freely Soluble	From 01 to 10 ml
Soluble	From 10 to 30 ml
Sparingly Soluble	From 30 to 100 ml
Slightly Soluble	From 100 to 1000 ml
Very Slightly Soluble	From 1000 to 10,000 ml
Practically Insoluble or Insoluble	10,000 and over.

3.0 IDENTIFICATION:

A) By TLC:

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 Thin-Layer Chromatographic

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Identification Test, 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) By HPLC: The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the assay.

4.0 ASSAY : 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 the gradient table below:

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.
[NOTE- Sonicate if necessary. Inject immediately or store in a refrigerator and use within 12 h.]
Sample solution: Constitute one container of Cefepime for Injection as directed on the label, and dilute

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using Solution B to 1 mg/ml of cefepime.

[NOTE-For products that are designed for administration with a syringe, withdraw the entire with drawable 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:

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1 ml/min

Injection size: 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 $C_{19}H_{24}N_6O_5S_2$ of 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 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)

Acceptance criteria: 90.0%-115.0%

5.0 UNIFORMITY OF DOSAGE UNITS: Meets the requirements.

6.0 ORGANIC IMPURITIES:

Procedure 1: 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 0.002N 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:

Mode: LC

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Detector: Conductivity
Column: 4.0-mm x 25-cm; 5-µm packing L76
Flow rate: 1 ml/min
Injection size: 10 µL
System suitability Sample: Standard solution
Suitability requirements
Relative standard deviation: NMT 4.0%
Analysis Samples: Standard solution and Sample solution
[Note-Record the chromatogram of the Sample solution for about 6 times the retention time of the N-methylpyrrolidine peak.]
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%
Procedure 2: Other Organic Impurities Solution A, Solution B, Solution C, Mobile phase, Chromatographic system, and Sample solution: Prepare as directed for 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
Suitability requirements
[NOTE-See Impurity Table 1 for the relative retention times.]
Resolution: NLT 2.0 between Cefepime related compound E and Cefepime related compound D
Tailing factor: NMT 1.5, 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 for each impurity
r_t = sum of the peak responses from the chromatogram
F =relative response factor from Impurity Table 1

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Acceptance criteria NOTE-The reporting level is 0.2% for Cefepime impurity C and 0.05% for all other related compounds.

Individual impurities: See Impurity Table 1.

Total impurities: NMT 2.2%. [NOTE-Total impurities include N-methylpyrrolidine.]

Impurity Table 1

Name	Relative Retention Time(%)	Relative Response Factor	Acceptance Criteria NMT (%)
Thiazoloxime acetaldehyde[d] (Cefepime related compound C)	0.6	0.63	0.5
E-Cefepime[f] (Cefepime related compound A)	2.7	0.71	0.5
Any individual unspecified impurity	_	1.0	0.5

7.0 INJECTION AND IMPLANTED DRUG PRODUCT: The following tests are performed to demonstrate suitability of constituted solutions prepared before administration. Constitute the solution as directed in the labeling supplied by the manufacturer:

- The solid dissolves completely, leaving no undissolved matter.
- The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly. Protein solutions may exhibit an inherent opalescence. The constituted solution is free from particulate matter that can be observed on visual inspection

8.0 BACTERIAL ENDOTOXINS TEST: : NMT 0.06 USP Endotoxin Unit/mg of cefepime.
Meets the requirements.
For analysis procedure refer to test should be performed as per micro SOP.

9.0 STERILITY TEST: Meets the requirements when tested as directed for Test for Sterility of the Product to Be Examined , Membrane Filtration.

10.0 pH: 4.0- 6.0, in a solution containing 100 mg/ml of cefepime.

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11.0 WATER DETERMINATION: Transfer 35 to 45 ml of methanol into titration vessel and titrate with KF reagent, which is standardized earlier, to the electrometric end point to consume any moisture present and refill the burette 0 mark again. Quickly, add 0.50 g of the substance, mix and titrate with the reagent to electrometric end point. The % of water content will display on the screen of the instrument. Calculate the percentage of water by following formula:-

$$\% \text{ Water Content} = \frac{V \times F \times 100}{A}$$

V= Volume of KF reagent consumed in ml.
F= Water equivalent factor of KF reagent m/ml.
A = Weight of sample in mg.

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