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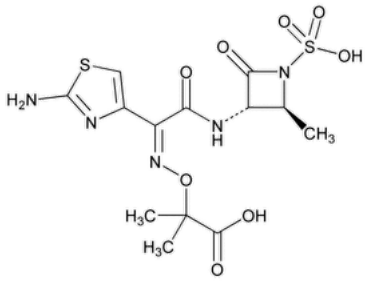
Aztreonam



$C_{13}H_{17}N_5O_8S_2$ 435.43

Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2*S*-[2α,3β(*Z*)]]-; (*Z*)-2-({[(2-Amino-4-thiazolyl){[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl}methylene]amino}oxy)-2-methylpropionic acid CAS RN®: 78110-38-0; UNII: G2B4VE5GH8.

DEFINITION

Aztreonam, which may be anhydrous or hydrated, contains NLT 92.0% and NMT 105.0% of aztreonam ($C_{13}H_{17}N_5O_8S_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) **:** If a difference appears in the IR spectra of the analyte and the standard, dissolve equal portions of the test specimen and the Reference Standard in equal volumes of methanol. [Note—To achieve a complete dissolution, it is suggested to use about 25 mL of methanol for each 50 mg of material, and stir the mixture for 40 min at room temperature.]

Evaporate the solutions to dryness under vacuum, and dry at 40° for 4 h under vacuum. Perform the test on the residues.

• **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**

[Note—Store the *System suitability solution*, *Standard solution*, and *Sample solution* at 5°, and protect from light to prevent isomerization of aztreonam *Z*-isomer to aztreonam *E*-isomer.]

Buffer: 6.8 mg/mL of monobasic potassium phosphate in water. Adjust with 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (1:4)

System suitability solution: 1 mg/mL of USP Aztreonam RS and 1 mg/mL of USP Aztreonam E-Isomer RS in *Mobile phase*

Standard solution: 1 mg/mL of USP Aztreonam RS in *Mobile phase*

Sample solution: 1 mg/mL of Aztreonam in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[Note—The relative retention times for aztreonam and aztreonam *E*-isomer are 1.0 and 1.8, respectively.]

Suitability requirements

Resolution: NLT 2.0 between aztreonam and aztreonam *E*-isomer, *System suitability solution*

Tailing factor: NMT 2 for aztreonam, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of aztreonam ($C_{13}H_{17}N_5O_8S_2$) in the portion of Aztreonam taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

P = potency of USP Aztreonam RS (µg/mg)

F = unit conversion factor, 0.001 mg/µg

Acceptance criteria: 92.0%–105.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%, the charred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid

• **Organic Impurities**

[Note—Store the *System suitability solution*, *Standard solution*, and *Sample solution* at 5°, and protect from light to prevent isomerization of aztreonam *Z*-isomer to aztreonam *E*-isomer.]

Mobile phase, System suitability solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Aztreonam taken:

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

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

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

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

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

P = potency of USP Aztreonam RS (µg/mg)

F = unit conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Open-ring aztreonam[a] and open-ring desulfated aztreonam[b,c]	0.55	1.0
Aztreonam (*Z*-isomer)	1.0	—
Desulfated aztreonam[d]	1.6	1.5
Aztreonam *E*-isomer[e]	1.8	0.5
Aztreonam ethyl ester[f]	3.9	1.5
Any individual unspecified impurity	—	0.1
Total impurities	—	3.0

[a] (2*S*,3*S*)-2-{(*Z*)-2-[2-Aminothiazol-4-yl]-2-[2-carboxypropan-2-yloxyimino]acetamido}-3-(sulfoamino)butanoic acid.

[b] (2*S*,3*S*)-3-Amino-2-{(*Z*)-2-[2-aminothiazol-4-yl]-2-[2-carboxypropan-2-yloxyimino]acetamido}butanoic acid.

[c] Open-ring aztreonam and open-ring desulfated aztreonam coelute. The limit is for the sum of these two impurities.

[d] (*Z*)-2-({[(2-Amino-4-thiazolyl){[(2*S*,3*S*)-2-methyl-4-oxo-3-azetidinyl]carbamoyl}methylene]amino}oxy)-2-methylpropionic acid.

[e] (*E*)-2-({[(2-Amino-4-thiazolyl){[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl}methylene]amino}oxy)-2-methylpropionic acid.

[f] Ethyl (*Z*)-2-({[(2-amino-4-thiazolyl){[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl}methylene]amino}oxy)-2-methylpropionate.

SPECIFIC TESTS

• **Sterility Tests ⟨71⟩, *Test for Sterility of the Product to Be Examined, Membrane Filtration*:** Where the label states that Aztreonam is sterile, it meets the requirements using *Fluid A*, to which 23.4 g of sterile arginine has been added to each 1000 mL.

• **Water Determination ⟨921⟩, *Method I*:** NMT 2.0%; if labeled as the hydrated form: 12.0%–18.0%. [Note—The term "hydrated form" refers to the α-form of Aztreonam, which is not a stoichiometric hydrate.]

• **Bacterial Endotoxins Test ⟨85⟩:** Where the label states that Aztreonam is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.17 USP Endotoxin Units/mg of aztreonam.

• **Limit of Alcohol**

[Note—This test is to be performed if alcohol is used while manufacturing Aztreonam.]

Standard solution: 0.004 mL/mL of alcohol from USP Alcohol Determination±Alcohol RS and 0.004 mL/mL of acetonitrile from USP Alcohol Determination—Acetonitrile RS in dimethylformamide. [Note—The *Standard solution* contains 0.4% alcohol and 0.4% acetonitrile.]

Sample solution: 80 mg/mL of Aztreonam and 0.004 mL/mL of acetonitrile in dimethylformamide. [Note—Dissolve Aztreonam in dimethylformamide using 20% of the final volume. Add a suitable aliquot of USP Alcohol Determination—Acetonitrile RS, and dilute with dimethylformamide to volume. The concentration of acetonitrile in the *Sample solution* is 0.4%.]

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m; phase G43

Film thickness: 3.0 µm

Temperatures

Injector: 210°

Detector: 280°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	5
50	10	200	4

Carrier gas: Helium

Linear velocity: 35 cm/s

Injection mode: Split

Injection volume: 0.5 µL

Injection type: Split ratio, 5:1

System suitability

Sample: *Standard solution*

[Note—The relative retention times for alcohol and acetonitrile are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2.0 between alcohol and acetonitrile

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of alcohol in the portion of Aztreonam taken:

$$\text{Result} = (R_U/R_S) \times [C_S \times (D/C_U)] \times F \times 100$$

R_U = peak response ratio of alcohol to acetonitrile from the *Sample solution*

R_S = peak response ratio of alcohol to acetonitrile from the *Standard solution*

C_S = concentration of alcohol in the *Standard solution* (mL/mL)

D = density of alcohol (g/mL)

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

F = unit conversion factor, 1000 mg/g

Acceptance criteria: NMT 4%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **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. Where it is the hydrated form, the label so indicates.

• **USP Reference Standards** ⟨11⟩

USP Alcohol Determination—Acetonitrile RS C_2H_3N 41.05

USP Alcohol Determination±Alcohol RS C_2H_5OH 46.07

USP Aztreonam RS

USP Aztreonam E-Isomer RS

(*E*)-2-({[(2-Amino-4-thiazolyl){[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl}methylene]amino}oxy)-2-methylpropionic acid.
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Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
AZTREONAM	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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