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Piperacillin and Tazobactam for Injection

DEFINITION

Piperacillin and Tazobactam for Injection contains amounts of Piperacillin Sodium and Tazobactam Sodium equivalent to NLT 90.0% and NMT 110.0% of the labeled amounts of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$), the labeled amounts representing proportions of piperacillin to tazobactam of 8:1. It may contain small amounts of a suitable buffer and stabilizer.

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the Assay.

ASSAY

PROCEDURE

Buffer: 27.6 g/L of monobasic sodium phosphate

Solution A: 80 mL of 40% aqueous tetrabutylammonium hydroxide diluted with water to 100 mL

Mobile phase: Methanol, water, *Buffer*, and *Solution A* (510:432:50:8). Adjust with phosphoric acid to a pH of 5.5.

Standard solution: 0.1 mg/mL of [USP Tazobactam RS](#) and 1 mg/mL of [USP Piperacillin RS](#) in *Mobile phase*. Refrigerate the *Standard solution* immediately after preparation and during analysis, using a refrigerated autosampler set at $5 \pm 3^\circ$. Analyze within 24 h of preparation.

Sample solution: Nominally 0.125 mg/mL of tazobactam and 1 mg/mL of piperacillin from Piperacillin and Tazobactam for Injection in *Mobile phase*. Refrigerate the *Sample solution* immediately after preparation and during analysis, using a refrigerated autosampler set at $5 \pm 3^\circ$. Analyze within 24 h of preparation.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm $\times$ 25-cm; 5- μ m packing L1

Flow rate: 1 mL/min

Injection volume: 10 μ L

Autosampler temperature: $5 \pm 3^\circ$

System suitability

[NOTE—The relative retention times for tazobactam and piperacillin are 0.36 and 1.0, respectively.]

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for tazobactam and piperacillin

Relative standard deviation: NMT 2.0% for tazobactam and piperacillin

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of piperacillin ($C_{23}H_{27}N_5O_7S$) in the portion of Piperacillin and Tazobactam 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 piperacillin from the *Sample solution*

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

C_S = concentration of [USP Piperacillin RS](#) in the *Standard solution* (mg/mL)

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

P = potency of piperacillin in [USP Piperacillin RS](#) ($\mu\text{g}/\text{mg}$)

F = conversion factor, 0.001 $\text{mg}/\mu\text{g}$

Calculate the percentage of the labeled amount of tazobactam ($\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_5\text{S}$) in the portion of Piperacillin and Tazobactam for Injection taken:

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

r_U = peak response of tazobactam from the *Sample solution*

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

C_S = concentration of [USP Tazobactam RS](#) in the *Standard solution* (mg/mL)

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

P = potency of tazobactam in [USP Tazobactam RS](#) (mg/mg)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- [UNIFORMITY OF DOSAGE UNITS \(905\)](#): Meets the requirements

IMPURITIES

• ORGANIC IMPURITIES, PROCEDURE 1

Organic Impurities, Procedure 1 is recommended when the impurity profile includes piperacillin impurities 4, 5, and 6.

Buffer: Dilute the contents of one vial of tetrabutylammonium hydrogen sulfate ion pairing reagent with water to 1 L.

Solution A: Phosphoric acid and water (1:4)

Mobile phase: Acetonitrile and *Buffer* (25:75). Adjust with *Solution A* to a pH of 3.8.

Diluent: Acetonitrile and water (25:75)

Standard stock solution 1: 60 $\mu\text{g}/\text{mL}$ of [USP Tazobactam Related Compound A RS](#) in *Diluent*

Standard stock solution 2: 0.5 mg/mL of [USP Tazobactam RS](#) in *Diluent*

Standard stock solution 3: 1.0 mg/mL of [USP Piperacillin RS](#) in acetonitrile and *Diluent* (1:24). Dissolve first in acetonitrile, using about 4% of the final volume, and dilute with *Diluent* to volume.

System suitability solution: 6 $\mu\text{g}/\text{mL}$ of tazobactam related compound A from *Standard stock solution 1* and 25 $\mu\text{g}/\text{mL}$ of tazobactam from *Standard stock solution 2* in *Diluent*

Standard solution: 25 $\mu\text{g}/\text{mL}$ of tazobactam from *Standard stock solution 2* and 0.2 mg/mL of piperacillin from *Standard stock solution 3* in *Mobile phase*. Refrigerate the solution immediately after preparation and during analysis, using a refrigerated autosampler set at $5 \pm 3^\circ$. Analyze within 24 h of preparation.

Sample solution: Nominally 25 $\mu\text{g}/\text{mL}$ of tazobactam and 0.2 mg/mL of piperacillin from Piperacillin and Tazobactam for Injection in *Mobile phase*. Refrigerate the solution immediately after preparation and during analysis, using a refrigerated autosampler set at $5 \pm 3^\circ$. Analyze within 24 h of preparation.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm $\times$ 15-cm; 3- μm packing L11

Flow rate: 1 mL/min

Injection volume: 20 μL

Autosampler temperature: $5 \pm 3^\circ$

System suitability

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

Suitability requirements

Resolution: NLT 3 between tazobactam related compound A and tazobactam, *System suitability solution*

Tailing factor: NMT 1.8 for tazobactam and piperacillin, *Standard solution*

Relative standard deviation: NMT 2% for tazobactam and piperacillin, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Piperacillin and Tazobactam for Injection taken:



$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (F_1/F_2) \times 100$$

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

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

C_S = concentration of [USP Piperacillin RS](#) in the *Standard solution* (mg/mL)

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

P = potency of [USP Piperacillin RS](#) (µg/mg)

F_1 = correction factor, 0.001 mg/µg

F_2 = relative response factor (see [Table 1](#))

Acceptance criteria: See [Table 1](#).

Table 1

Name	Relative Retention Time	Relative Response Factor ^a	Acceptance Criteria, NMT (%) ^a
Tazobactam related compound A ^b	0.12	0.75	1.0
Tazobactam	0.25	—	—
Piperacillin impurity 4 ^c	0.31	1.0	1.0
Piperacillin penilloic acid ^{d,e}	0.36	1.0	1.0
Piperacillin penicilloic acid ^{d,f}	0.51	0.56	5.0
Acetylated penicilloic acid of piperacillin ^g	0.55	1.0	1.0
Piperacillin impurity 5 ^c	0.62	1.0	1.0
Piperacillin impurity 6 ^c	0.67	1.0	1.0
Piperacillin	1.0	—	—
Any individual unspecified impurity	—	1.0	1.0
Total impurities ^h	—	—	5.0

^a Calculated relative to the peak area of piperacillin.

^b (2S,3S)-2-Amino-3-methyl-3-sulfinyl-4-((1H-1,2,3-triazol-1-yl)butyric acid.

^c Specified unidentified impurities.

^d This compound has two epimers that usually co-elute but that may be separated as a result of minor changes in the chromatographic conditions.

^e (4S)-2-([2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl)-5,5-dimethylthiazolidine-4-carboxylic acid.

^f (2R,4S)-2-((1R)-Carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl)-5,5-dimethylthiazolidine-4-carboxylic acid.

^g (2*R*,4*S*)-3-Acetyl-2-[(1*R*)-carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^h Total impurities does not include piperacillin penicilloic acid.

• **ORGANIC IMPURITIES, PROCEDURE 2**

Organic Impurities, Procedure 2 is recommended when the impurity profile includes piperacillin dimer ethyl ester and piperacillin dimer thiazolamide derivative.

Solution A: 3.12 g/L of monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 3.5.

Solution B: Methanol

Mobile phase: See [Table 2](#).

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
5	85	15
10	65	35
35	55	45
60	35	65
65	90	10
75	90	10

System suitability solution 1: 10 µg/mL of [USP Amoxicillin Related Compound A RS](#) and 6 µg/mL of [USP Tazobactam Related Compound A RS](#) in *Solution A*. Refrigerate *System suitability solution 1* immediately after preparation and during analysis, using a refrigerated autosampler set at 5 ± 3°. Analyze within 24 h of preparation.

System suitability solution 2: 0.2 mg/mL each of [USP Piperacillin RS](#) and [USP Tazobactam RS](#) in a mixture of methanol and *Solution A* (30:70). Prepare the solution by dissolving the compounds in methanol and diluting with *Solution A* to volume. Refrigerate *System suitability solution 2* immediately after preparation and during analysis, using a refrigerated autosampler set at 5 ± 3°. Analyze within 24 h of preparation.

Sample solution: Nominally 2 mg/mL of piperacillin and 0.25 mg/mL of tazobactam from Piperacillin and Tazobactam for Injection in *Solution A*. Refrigerate the *Sample solution* immediately after preparation and during analysis, using a refrigerated autosampler set at 5 ± 3°. Analyze within 24 h of preparation.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 220 nm

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

Temperatures

Column: 30°

Autosampler: 5 ± 3°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution 1* and *System suitability solution 2*

Suitability requirements

Resolution: NLT 1.5 between tazobactam related compound A and amoxicillin related compound A, *System suitability solution 1*

Tailing factor: NMT 2.0 for the piperacillin and tazobactam peaks, *System suitability solution 2*

Relative standard deviation: NMT 10.0% for the piperacillin and tazobactam peaks, *System suitability solution 2*

Analysis

Sample: *Sample solution*