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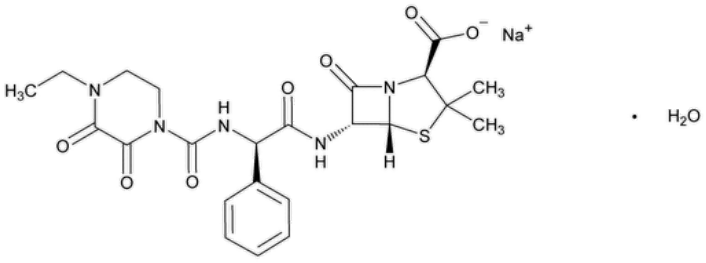
Piperacillin Sodium



$C_{23}H_{26}N_5NaO_7S$ 539.54

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2*S*-[2α,5α,6β(*S**)]];

Sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate CAS RN®: 59703-84-3.

DEFINITION

Piperacillin Sodium has a potency equivalent to NLT 863 µg/mg and NMT 1007 µg/mg of piperacillin ($C_{23}H_{27}N_5O_7S$), calculated on the anhydrous basis.

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, and the chromatogram compares qualitatively to that of the *Standard solution*, as obtained in the *Assay*.

• **B.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sodium*:** Meets the requirements

Add the following:

▲• **C.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Dec-2019)

ASSAY

Change to read:

• **Procedure**

Mobile phase: Methanol, water, 0.2 M monobasic sodium phosphate, and 0.4 M tetrabutylammonium hydroxide (450:447:100:3). Adjust with phosphoric acid to a pH of 5.50.

System suitability solution: 0.1 mg/mL of USP Ampicillin RS and 0.2 mg/mL of USP Piperacillin RS in *Mobile phase*

Standard solution 1: 0.4 mg/mL of USP Piperacillin RS in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Sample solution: 0.4 mg/mL of Piperacillin Sodium in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm. ▲For *Identification C*, use a diode array detector in the range of 190–400 nm.▲ (USP 1-Dec-2019)

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 16 between ampicillin and piperacillin, *System suitability solution*

Tailing factor: NMT 1.2 for piperacillin, *System suitability solution*

Relative standard deviation: NMT 2% for piperacillin, *Standard solution 1*

Analysis

Samples: *Standard solution 1* and *Sample solution*

Calculate the potency, in µg/mg, of piperacillin ($C_{23}H_{27}N_5O_7S$) in the portion of Piperacillin Sodium taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from *Standard solution 1*

C_S = concentration of USP Piperacillin RS in *Standard solution 1* (mg/mL)

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

P = potency of piperacillin in USP Piperacillin RS (µg/mg)

Acceptance criteria: 863–1007 µg/mg on the anhydrous basis

IMPURITIES

• **PIPERACILLIN PENICILLOIC ACID AND ACETYLATED PENICILLOIC ACID OF PIPERACILLIN**

Mobile phase, System suitability solution, Standard solution 1, and **Sample solution:** Prepare as directed in the *Assay*.

Standard solution 2: 0.04 mg/mL of USP Piperacillin RS in *Mobile phase*. Dissolve in a few drops of methanol, and dilute with *Mobile phase* to volume. Use this solution within 1 h.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 16 between ampicillin and piperacillin, *System suitability solution*

Tailing factor: NMT 1.2 for piperacillin, *System suitability solution*

Relative standard deviation: NMT 2% for piperacillin, *Standard solution 1*

Analysis

Samples: *Sample solution* and *Standard solution 2*

Calculate the percentages of piperacillin penicilloic acid and acetylated penicilloic acid of piperacillin in the portion of Piperacillin Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (1/F_1) \times F_2 \times 100$$

r_U = peak response of piperacillin penicilloic acid or acetylated penicilloic acid of piperacillin from the *Sample solution*

r_S = peak response of piperacillin from *Standard solution 2*

C_S = concentration of USP Piperacillin RS in *Standard solution 2* (mg/mL)

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

P = potency of piperacillin in USP Piperacillin RS (µg/mg)

F_1 = relative response factor (see *Table 1*)

F_2 = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Piperacillin related compound E[a,b]	0.24	—	—
Ampicillin	0.31	—	—
Acetylated penicilloic acid of piperacillin[c]	0.37	1.1	1.0
Piperacillin penicilloic acid[d]	0.62	0.7	3.5
Piperacillin	1.0	—	—

[a] This impurity is not to be reported.

[b] 1-Ethyl-2,3-piperazinedione.

[c] (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.

[d] (2*R*,4*S*)-2-{(1*R*)-Carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 400 mg/mL

Acceptance criteria: 5.5–7.5

• **Water Determination** ⟨921⟩, *Method I*

Test preparation: Prepare as described for hygroscopic substances.

Acceptance criteria: NMT 1.0%

Change to read:

• **Bacterial Endotoxins Test** ⟨85⟩**:** ▲Where the label states that Piperacillin Sodium must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Piperacillin is used can be met.▲ (USP 1-Dec-2019)

Change to read:

• **Sterility Tests** ⟨71⟩**:** ▲It meets the requirements where the label states that Piperacillin Sodium is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms.▲ (USP 1-Dec-2019)

ADDITIONAL REQUIREMENTS

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

Change to read:

• **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 Piperacillin Sodium must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled.▲ (USP 1-Dec-2019)

• **USP Reference Standards** ⟨11⟩

USP Ampicillin RS

USP Piperacillin RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
PIPERACILLIN SODIUM	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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