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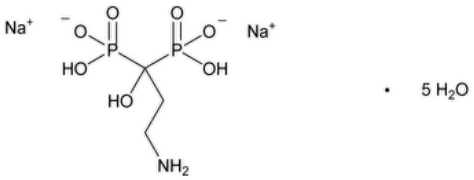
Pamidronate Disodium



$C_3H_9NNa_2O_7P_2 \cdot 5H_2O$ 369.11

Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt, pentahydrate;

Disodium dihydrogen (3-amino-1-hydroxypropylidene)diphosphonate, pentahydrate CAS RN®: 109552-15-0; UNII: 8742T8ZQZA.

Anhydrous

$C_3H_9NNa_2O_7P_2$ 279.03 CAS RN®: 57248-88-1; UNII: C7S8VWP5DH.

DEFINITION

Pamidronate Disodium contains NLT 98.0% and NMT 102.0% of Pamidronate Disodium ($C_3H_9NNa_2O_7P_2$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-Aug-2022)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sodium*:** Meets the requirements

ASSAY

Change to read:

- **Procedure**

Mobile phase: 0.47 mL of formic acid, anhydrous in 2500 mL of water. Adjust with 2 N sodium hydroxide to a pH of 3.5. [Note—The small amounts of formic acid have a strong influence on the retention times.]

Standard solution: 2.0 mg/mL of USP Pamidronate Disodium RS in water

Sample solution: 2.0 mg/mL of Pamidronate Disodium in water

Chromatographic system

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

Mode: LC

Detector: Refractive index

Column: 4.6-mm × 10-cm; packing L23. ▲[Note—It is required to saturate the column for at least 12 h before starting analysis.]▲ (USP 1-Aug-2022)

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.3–1.2

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of pamidronate disodium ($C_3H_9NNa_2O_7P_2$) in the portion of Pamidronate Disodium taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Change to read:

• **Organic Impurities, Procedure 1**

▲**Buffer:** 2.94 g/L of sodium citrate dihydrate and 1.42 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 8.0.

Solution A: Acetonitrile and *Buffer* (15:85)

Solution B: Acetonitrile and *Buffer* (70:30)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	50	50
25	0	100
27	100	0
42	100	0

Diluent: 29.4 g/L of sodium citrate dihydrate in water

Derivatizing reagent solution: 4.0 mg/mL of 9-fluorenylmethyl chloroformate in acetonitrile. [Note—Prepare fresh prior to use.]

Borate solution: 19.1 mg/mL of sodium borate in water

Standard stock solution: 0.6 µg/mL of USP Pamidronate Disodium RS in *Diluent*

Standard solution: 0.15 µg/mL of USP Pamidronate Disodium RS from the *Standard stock solution* as follows. Transfer 5.0 mL of *Standard stock solution* into a 50-mL polypropylene screw-cap centrifuge tube containing about 5.0 mL of *Borate solution* and 5.0 mL of acetonitrile. Add 5.0 mL of *Derivatizing reagent solution* and shake for 45 s. Allow the solution to stand at room temperature for 30 min. Add 20 mL of methylene chloride and shake for 1 min. Centrifuge for 5–10 min and use a portion of the clear supernatant layer.

Sensitivity stock solution: 0.3 µg/mL of USP Pamidronate Disodium RS in *Diluent*, from the *Standard stock solution*

Sensitivity solution: 0.075 µg/mL of USP Pamidronate Disodium RS from the *Sensitivity stock solution* as follows. Transfer 5.0 mL of *Sensitivity stock solution* into a 50-mL polypropylene screw-cap centrifuge tube containing about 5.0 mL of *Borate solution* and 5.0 mL of acetonitrile. Add 5.0 mL of *Derivatizing reagent solution* and shake for 45 s. Allow the solution to stand at room temperature for 30 min. Add 20 mL of methylene chloride and shake for 1 min. Centrifuge for 5–10 min and use a portion of the clear supernatant layer.

Sample stock solution: 0.6 mg/mL of Pamidronate Disodium in *Diluent*

Sample solution: 0.15 mg/mL of Pamidronate Disodium from the *Sample stock solution* as follows. Transfer 5.0 mL of the *Sample stock solution* into a 50-mL polypropylene screw-cap centrifuge tube containing about 5.0 mL of *Borate solution* and 5.0 mL of acetonitrile. Add 5.0 mL of *Derivatizing reagent solution* and shake for 45 s. Allow the solution to stand at room temperature for 30 min. Add 20 mL of methylene chloride and shake for 1 min. Centrifuge for 5–10 min and use a portion of the clear supernatant layer.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.1-mm × 25-cm; 5-µm packing L21

Column temperature: 45°

Flow rate: 1.8 mL/min

Injection volume: 50 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Relative standard deviation: NMT 10.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Pamidronate Disodium taken:

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

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

r_S = peak response of pamidronate disodium from the *Standard solution*

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

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Pamidronate disodium	1.0	—	—
Beta alanine[a]	1.95	2.5	0.15
Any unknown impurity	—	1.0	0.10
Total impurities[b]	—	—	1.0▲ (USP 1-Aug-2022)

[a] 3-Aminopropanoic acid.

[b] Including phosphate and phosphite.

Change to read:

• **Organic Impurities, Procedure 2: Phosphate and Phosphite**

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

Standard stock solution 1: 0.3 mg/mL of ▲USP Phosphoric Acid RS▲ (USP 1-Aug-2022) in water

Standard stock solution 2: 0.25 mg/mL of phosphorous acid in water

Standard solution: 12.0 µg/mL of USP Phosphoric Acid RS and 10.0 µg/mL of phosphorous acid from *Standard stock solution 1* and *Standard stock solution 2* in water

System suitability

Sample: *Standard solution*

[Note—The elution order is phosphate, followed by phosphite.]

Suitability requirements

Resolution: NLT 2.5 between phosphate and phosphite

Relative standard deviation: NMT 10.0% for phosphate and NMT 20.0% for phosphite

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of phosphate as orthophosphoric acid in the portion of Pamidronate Disodium taken:

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

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

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

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

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

Calculate the percentage of phosphite as phosphorous acid in the portion of Pamidronate Disodium taken:

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

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

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

C_S = concentration of phosphorous acid in the *Standard solution* (mg/mL)

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

Acceptance criteria

Phosphate: NMT 0.50%

Phosphite: NMT 0.50%

Total phosphate and phosphite: NMT 0.50%

Total other impurities (excluding beta alanine, phosphate, and phosphite): NMT 0.50%

SPECIFIC TESTS

• **Clarity and Color of Solution**

Sample solution 1: 20 mg/mL of Pamidronate Disodium in water with gentle warming. Allow to cool to room temperature.

Sample solution 2: 40 mg/mL of Pamidronate Disodium in 2 N sodium hydroxide with gentle warming. Allow to cool to room temperature.

Instrumental conditions

Mode: UV-Vis

Analytical wavelength: 420 nm

Path length: 4 cm

Blank: Water (*Sample solution 1*) and 2 N sodium hydroxide (*Sample solution 2*)

Analysis

Samples: *Sample solution 1* and *Sample solution 2*

Examine *Sample solution 1* and *Sample solution 2*.

Acceptance criteria: The solutions are clear. The absorbance of each solution is NMT 0.10.

• **pH ⟨791⟩:** 7.8–8.8, in a solution (1 in 100)

Add the following:

▲• **Bacterial Endotoxins Test ⟨85⟩:** Where the label states that pamidronate disodium must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxin is such that the requirement in the relevant dosage form monograph(s) in which pamidronate disodium is used can be met.▲ (USP 1-Aug-2022)

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 1000 cfu/g, and the total combined yeasts and molds count does not exceed 100 cfu/g.

• **Water Determination ⟨921⟩, *Method I*:** 23.0%–25.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at a temperature not exceeding 30°.

Add the following:

▲• **Labeling:** Where Pamidronate Disodium 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-Aug-2022)

Change to read:

• **USP Reference Standards** ⟨11⟩

▲▲ (USP 1-Aug-2022)

USP Pamidronate Disodium RS

▲ USP Phosphoric Acid RS▲ (USP 1-Aug-2022)

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

Topic/Question	Contact	Expert Committee
PAMIDRONATE DISODIUM	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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