SODIUM ALENDRONATE

Natrii alendronas

\[ \text{C}_4\text{H}_7\text{NNaO}_7\text{P}_2\cdot3\text{H}_2\text{O} \]  \hspace{1cm} M, 325.1

DEFINITION
Sodium alendronate contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt, calculated with reference to the dried substance.

CHARACTERS
A white or almost white, crystalline powder, soluble in water, very slightly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION
A. Examine by infrared absorption spectrophotometry (2.2.24), comparing with the spectrum obtained with sodium alendronate CRS. Examine the substances prepared as discs.

B. It gives reaction (a) of sodium (2.3.1).

TESTS
Solution S. Dissolve 0.5 g in carbon dioxide-free water \( R \) prepared from distilled water \( R \) and dilute to 50 ml with the same solvent.

Appearance of solution. Solution S is clear (2.2.1) and not more intensely coloured than reference solution B1 or BY1 (2.2.2, Method II).

\( \text{pH} \) (2.2.3). The \( \text{pH} \) of solution S is 4.0 to 5.0.

4-aminobutanoic acid. Examine by thin-layer chromatography (2.2.27), using a TLC silica gel plate \( R \). Test solution. Dissolve 0.10 g of the substance to be examined in water \( R \) and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 0.10 g of 4-aminobutanoic acid \( R \) in water \( R \) and dilute to 200 ml with the same solvent. Reference solution (b). Dilute 1 ml of reference solution (a) to 10 ml with water \( R \).

Apply to the plate 5 \( \mu l \) of the test solution and 5 \( \mu l \) of reference solution (b). Allow the plate to dry in air. Develop over a path of 15 cm using a mixture of 20 volumes of water \( R \), 20 volumes of glacial acetic acid \( R \) and 60 volumes of butanol \( R \). Dry the plate in a current of warm air. Spray with ninhydrin solution \( R \) and heat at 100 °C to 105 °C for 15 min. Any spots corresponding to 4-aminobutanoic acid in the chromatogram obtained with the test solution are not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent).

Phosphate and phosphate. Examine the chromatograms obtained in the assay. In the chromatogram obtained with the test solution: the area of any peak corresponding to phosphate is not greater than that of the peak due to phosphate in the chromatogram obtained with reference solution (d) (0.5 per cent); the area of any peak corresponding

ASSAY
Dissolve 0.250 g in 50 ml of anhydrous acetic acid \( R \), add 5 ml of acetic anhydride \( R \) and allow to stand for 30 min. Using 0.3 ml of naphtholbenzoin solution \( R \) as indicator, titrate with 0.1 M perchloric acid until a green colour is obtained.

1 ml of 0.1 M perchloric acid is equivalent to 8.20 mg of \( \text{C}_2\text{H}_7\text{NaO}_2 \).
to phosphite is not greater than that of the peak due to phosphite in the chromatogram obtained with reference solution (d) (0.5 per cent).

**Heavy metals** (2.4.8). 1.0 g complies with limit test F for heavy metals (20 ppm). Prepare the standard using 2 ml of lead standard solution (10 ppm Pb) R.

**Loss on drying** (2.2.32): 16.1 per cent to 17.1 per cent, determined on 1.000 g by drying in an oven at 140 °C to 145 °C.

**ASSAY**

Examine by liquid chromatography (2.2.29).

**Test solution.** Dissolve 50.0 mg of the substance to be examined in water R and dilute to 25.0 ml with the same solvent.

**Reference solution (a).** Dissolve 50.0 mg of sodium alendronate CRS in water R and dilute to 25.0 ml with the same solvent.

**Reference solution (b).** Dissolve 3.0 g of phosphoric acid R in water R and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with water R.

**Reference solution (c).** Dissolve 2.5 g of phosphorous acid R in water R and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with water R.

**Reference solution (d).** Mix 2.0 ml of reference solution (b) and 2.0 ml of reference solution (c) and dilute to 50.0 ml with water R.

The chromatographic procedure may be carried out using:

- a column 0.15 m long and 4.6 mm in internal diameter packed with anion exchange resin R1 (7 µm),
- as mobile phase at a flow rate of 1.2 ml/min a solution of 0.2 ml of anhydrous formic acid R in 1000 ml of water R, adjusted to pH 3.5 with 2 M sodium hydroxide solution, 3 min, cool, add 5 ml of alcohol R, shake with 15 ml of di-isopropyl ether R. Carry out a blank test. The upper layer obtained with the substance to be examined exhibits a deeper bluish-red colour than that obtained with the blank.

D. It complies with the test for sulphated ash. The residue obtained, dissolved in 2 ml of water R, gives reaction (a) of sodium (2.3.1).

**TESTS**

**Solution S.** Dissolve 0.10 g in water R, with constant stirring, dilute to 30 ml with the same solvent and allow to stand for 1 h.

**Appearance of solution.** Dilute 1 ml of solution S to 10 ml with water R. The solution is not more opalescent than reference suspension II (2.2.I) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (2.2.2, Method II).

**Chlorides.** Not more than 1.0 per cent. To 2.50 g add 50 ml of dilute nitric acid R, shake for 1 h and dilute to 100.0 ml with dilute nitric acid R. Filter. To 50.0 ml of the filtrate add 10.0 ml of 0.1 M silver nitrate solution R, 5 ml of hydrochloric acid R. Boil for 3 min, cool, add 5 ml of water R, and shake with 15 ml of di-isopropyl ether R. Carry out a blank test. The upper layer obtained with the substance to be examined is insoluble in alcohol.

**Calcium.** Not more than 1.5 per cent of Ca, determined by atomic absorption spectrometry (2.2.23, Method II).

**Test solution.** Dissolve 0.10 g of the substance to be examined in 50 ml of dilute ammonia R2, heating on a water-bath. Add and dilute to 100.0 ml with distilled water R (solution (a)). Dilute 0.3 ml of solution (a) to 100.0 ml with distilled water R.

**Reference solutions.** Prepare three reference solutions in the same manner as the test solution but add 0.75 ml, 1.0 ml and 1.5 ml respectively of calcium standard solution (100 ppm Ca) R to the 3.0 ml of solution (a).