Edition: BP 2025 (Ph. Eur. 11.6 update)

Alendronic Acid Tablets

General Notices

Sodium Alendronate Tablets

Action and use

Bisphosphonate; treatment of osteoporosis.

DEFINITION

Alendronic Acid Tablets contain Sodium Alendronate Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of alendronic acid, $C_4H_{13}NO_7P_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Mix a quantity of the powdered tablets containing the equivalent of 76 mg of alendronic acid with 50 mL of *water* for 30 minutes with the aid of ultrasound and occasional shaking, and filter.
(2) 0.2% w/v of *sodium alendronate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *cellulose*.
(b) Use the mobile phase as described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in a current of warm air, spray with *ninhydrin solution*, heat at 100° to 105° for 15 minutes and examine.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 8 volumes of 2.5% v/v *trichloroacetic acid* and 11 volumes of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes, withdraw a sample of the medium and filter (Whatman GF/C is suitable). Use the filtered sample diluted with the dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.00084% w/v of alendronic acid.
(2) 0.0011% w/v of *sodium alendronate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *anion exchange resin* (7 µm) (Allsep Anion is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a refractive index detector, maintained at 40°.
(f) Inject 100 µL of each solution.

MOBILE PHASE

0.02% v/v of *formic acid*, pH adjusted to 3.5 with *2M sodium hydroxide*.

DETERMINATION OF CONTENT

Calculate the total content of $C_4H_{13}NO_7P_2$ in the medium using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS*. Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

LIMITS

The amount of alendronic acid released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Buffer solution Prepare a solution containing 0.294% w/v of *sodium citrate* and 0.142% w/v of *anhydrous disodium hydrogen orthophosphate*, adjusted to pH 8.0 using *orthophosphoric acid* and filter.

Solution A 2.94% w/v of *sodium citrate* in *water*.

Solution B 1.91% w/v of *sodium borate* in *water*.

Solution C 0.02% w/v of *(9-fluorenyl)methyl chloroformate* in *acetonitrile*. Prepare immediately before use.

(1) Mix a quantity of the powdered tablets containing the equivalent of 23 mg of alendronic acid with solution A and make up to 50 mL with the same solvent. Mix and filter (Whatman GF/C is suitable), discarding the first 5 mL of filtrate. To 5 mL of the filtrate in a screw cap centrifuge tube add 5 mL of solution B and 10 mL of solution C, shake for 1 minute and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute; centrifuge and use the aqueous layer.
(2) To 5 mL of a 0.0003% w/v solution of *4-aminobutanoic acid* in solution A in a screw cap centrifuge tube, add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes, add

20 mL of *dichloromethane* and shake vigorously for 1 minute, centrifuge and use the aqueous layer.
(3) To 5 mL of a solution containing 0.06% w/v of *sodium alendronate BPCRS* and 0.01% w/v of *4-aminobutanoic acid* in solution A in a screw cap centrifuge tube add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes, add 20 mL of *dichloromethane* and shake vigorously for 1 minute; centrifuge and use the aqueous layer.
(4) To 5 mL of a solution containing 0.00012% of *sodium alendronate BPCRS* in solution A in a screw cap centrifuge tube, add 5 mL of solution B and 10 mL of solution C, shake for 45 seconds and allow to stand at room temperature for 30 minutes. Add 20 mL of *dichloromethane* and shake vigorously for 1 minute, centrifuge and use the aqueous layer.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.1 mm) packed with *styrene-divinylbenzene copolymer* (10 µm) (Hamilton PRP-1 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.8 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 266 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 3 volumes of *acetonitrile* and 17 volumes of buffer solution.

Mobile phase B 3 volumes of buffer solution and 7 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-15	100→50	0→50	linear gradient
15-25	50→0	50→100	linear gradient
25-27	0→100	100→0	linear gradient
27-32	100	0	re-equilibration

The retention time of the peaks due to alendronic acid and aminobutanoic acid, as their derivatives, are about 5 minutes and about 9.5 minutes respectively.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the two principal peaks is at least 10.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminobutanoic acid is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Impurities B and C

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing the equivalent of 0.1 g of alendronic acid, add 20 mL of *water* and mix with the aid of ultrasound for 30 minutes. Add sufficient *water* to produce 25 mL and filter (Whatman GF/C is suitable).
(2) 0.0024% w/v of *orthophosphoric acid* (impurity B) and 0.002% w/v of *phosphorous acid* (impurity C).

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used. Allow the chromatography to proceed for twice the retention time of the principal peak.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to alendronic acid (retention time, about 17 minutes) are: impurity B, about 1.3 and impurity C, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *signal-to-noise* ratios of the peaks due to impurity B and impurity C are at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity B or impurity C is not greater than the area of any corresponding peak in the chromatogram obtained with solution (2) (0.5%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix a quantity of the powdered tablets containing the equivalent of 50 mg of alendronic acid with 20 mL of *water* for 30 minutes with the aid of ultrasound and occasional shaking, and agitate until cool, add sufficient *water* to produce 25 mL, mix and filter (Whatman GF/C is suitable).
(2) 0.22% w/v of *sodium alendronate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_4H_{13}NO_7P_2$ in the tablets using the declared content of $C_4H_{12}NNaO_7P_2$ in *sodium alendronate BPCRS*. Each mg of $C_4H_{12}NNaO_7P_2$ is equivalent to 0.9189 mg of $C_4H_{13}NO_7P_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of alendronic acid.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Sodium Alendronate Trihydrate.