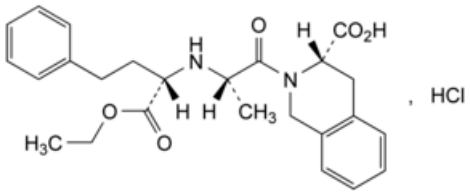
Edition: BP 2025 (Ph. Eur. 11.6 update)

Quinapril Hydrochloride

General Notices

(Ph. Eur. monograph 1763)



$C_{25}H_{31}ClN_2O_5$ 475.0 *82586-55-8*

Action and use

Angiotensin converting enzyme inhibitor.

Preparation

Quinapril Tablets

Ph Eur

DEFINITION

(3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride.

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white or slightly pink, hygroscopic powder.

Solubility

Freely soluble in water and in ethanol (96 per cent), very slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison quinapril hydrochloride CRS.

B. Specific optical rotation (see Tests).
C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Specific optical rotation (2.2.7)

+ 14.4 to + 16.6 (anhydrous substance).

Dissolve 0.500 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Diastereoisomers

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use*.

Solvent mixture Adjust 500 mL of the mobile phase to pH 6.5 with *concentrated ammonia R*.

Test solution Dissolve 100 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of *quinapril for peak identification CRS* (containing impurities G, H and I) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 25 °C.

Mobile phase Mix 260 mL of *tetrahydrofuran R* (non-stabilised) with 740 mL of a freshly prepared solution containing 1.08 g/L of *sodium octanesulfonate R* and 2.88 g/L of *ammonium dihydrogen phosphate R*, previously adjusted to pH 4.5 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

Run time 3.5 times the retention time of quinapril.

Identification of impurities Use the chromatogram supplied with *quinapril for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G, H and I.

Relative retention With reference to quinapril (retention time = about 18 min): impurity G = about 0.9; impurity H = about 1.2; impurity I = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity G and quinapril;

— *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity H and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to quinapril.

Limits:

— *impurities G, H, I*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mix 40 volumes of acetonitrile R1 and 60 volumes of a 2.88 g/L solution of ammonium dihydrogen phosphate R previously adjusted to pH 6.5 with dilute ammonia R1.

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of quinapril for system suitability CRS (containing impurities A, C, D, E and G) in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (c) In order to prepare impurity M *in situ*, dissolve 250 mg of the substance to be examined in methylene chloride R and dilute to 5.0 mL with the same solvent. Expose this solution to a source of ultraviolet light for 2.5 h and evaporate the solvent. Dissolve 40 mg of the remaining substance in the solvent mixture and dilute to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: end-capped octylsilyl silica gel for chromatography R (5 µm).

Temperature:

— *column*: 30 °C;

— *autosampler*: 5 °C.

Mobile phase acetonitrile R1, 5.77 g/L solution of sodium dodecyl sulfate R adjusted to pH 2.2 with phosphoric acid R (48:52 *V/V*).

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 214 nm.

Injection 10 µL.

Run time 3 times the retention time of quinapril.

Identification of impurities Use the chromatogram supplied with quinapril for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, C, D, E and G; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity M.

Relative retention With reference to quinapril (retention time = about 12 min): impurity A = about 0.1; impurity C = about 0.3; impurity D = about 0.4; impurity M = about 0.7; impurities G + H = about 0.9; impurity E = about 2.3.

System suitability Reference solution (b):

— resolution: minimum 1.5 between the peaks due to impurities C and D; minimum 1.5 between the peaks due to impurity G and quinapril.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity E by 1.5;

— *impurities C, D*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurities E, M*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to impurities G + H.

Water (*2.5.12*)

Maximum 1.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.75 mg of $C_{25}H_{31}ClN_2O_5$.

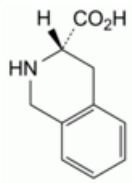
STORAGE

In an airtight container at a temperature of 2 °C to 8 °C.

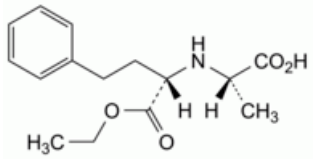
IMPURITIES

Specified impurities A, C, D, E, G, H, I, M.

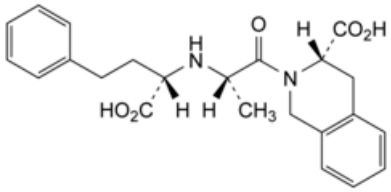
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, J.



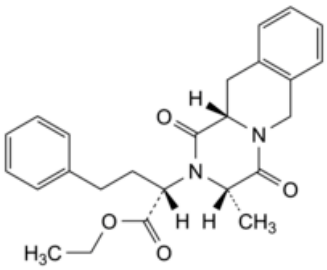
A. (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



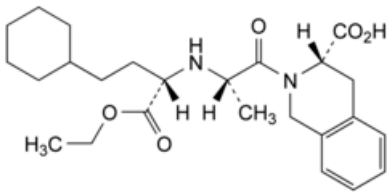
B. (2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



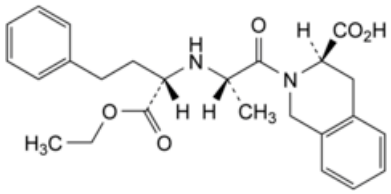
C. (3*S*)-2-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



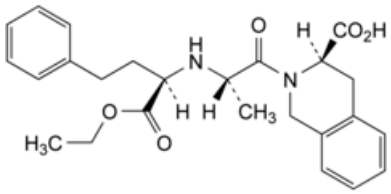
D. ethyl (2*S*)-2-[(3*S*,11a*S*)-3-methyl-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl]-4-phenylbutanoate,



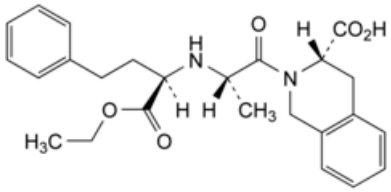
E. (3*S*)-2-[(2*S*)-2-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



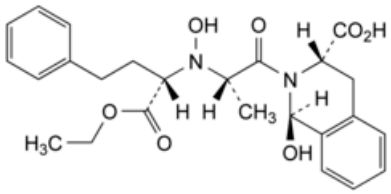
G. (3*R*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



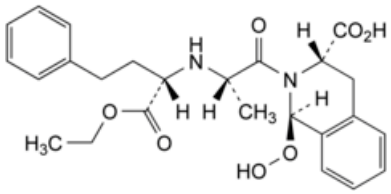
H. (3*R*)-2-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



I. (3*S*)-2-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



J. (1*R*,3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl](hydroxy)amino]propanoyl]-1-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,



M. (1*R*,3*S*)-2-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-1-hydroperoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

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