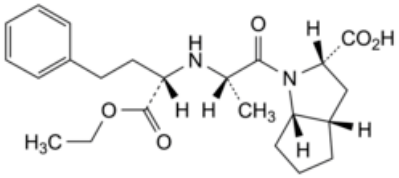
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ramipril

General Notices

(Ph. Eur. monograph 1368)



$C_{23}H_{32}N_2O_5$ 416.5 *87333-19-5*

Action and use

Angiotensin converting enzyme inhibitor.

Preparations

Ramipril Capsules

Ramipril Tablets

Ph Eur

DEFINITION

(2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

Content

98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in methanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).
B. Infrared absorption spectrophotometry (2.2.24).

Comparison *ramipril CRS*.

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, *Method II*).

Dissolve 0.1 g in *methanol R* and dilute to 10.0 mL with the same solvent.

Specific optical rotation (2.2.7)

+ 32.0 to + 38.0 (dried substance).

Dissolve 0.250 g in a mixture of 14 volumes of *hydrochloric acid R1* and 86 volumes of *methanol R* and dilute to 25.0 mL with the same mixture of solvents.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dissolve 2 mg of *ramipril impurity A CRS*, 2 mg of *ramipril impurity B CRS*, 2 mg of *ramipril impurity C CRS* and 2 mg of *ramipril impurity D CRS* in mobile phase A and dilute to 25 mL with mobile phase A. To 1 mL of this solution, add 5 mL of the test solution and dilute to 10 mL with mobile phase B.

Reference solution (b) Dilute 5.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase B.

Reference solution (c) Dilute 1.0 mL of reference solution (b) to 10.0 mL with mobile phase B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 65 °C.

Mobile phase:

— *mobile phase A*: dissolve 2.0 g of *sodium perchlorate R* in a mixture of 0.5 mL of *triethylamine R* and 800 mL of *water for chromatography R*; adjust to pH 3.6 with *phosphoric acid R* and add 200 mL of *acetonitrile R1*;

— *mobile phase B*: dissolve 2.0 g of *sodium perchlorate R* in a mixture of 0.5 mL of *triethylamine R* and 300 mL of *water for chromatography R*; adjust to pH 2.6 with *phosphoric acid R* and add 700 mL of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 6	90	10
6 - 7	90 → 75	10 → 25
7 - 20	75 → 65	25 → 35

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
20 - 30	65 → 25	35 → 75
30 - 50	25	75

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Equilibration With the mobile phase at the initial composition for at least 35 min; if a suitable baseline cannot be obtained, use another grade of triethylamine.

Injection 10 µL.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to ramipril (retention time = about 18 min): impurity A = about 0.8; impurity B = about 1.3; impurity C = about 1.5; impurity D = about 1.7.

System suitability:

— *resolution*: minimum 3.0 between the peaks due to impurity A and ramipril in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c);

— *symmetry factor*: 0.8 to 2.0 for the peak due to ramipril in the chromatogram obtained with the test solution.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.4;

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

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

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

— *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.2 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 25 mL of *methanol R* and add 25 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 41.65 mg of $C_{23}H_{32}N_2O_5$.

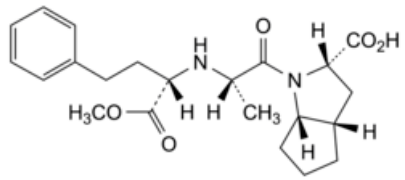
STORAGE

Protected from light.

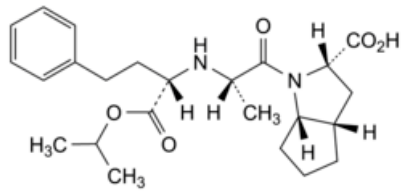
IMPURITIES

Specified impurities A, B, C, D.

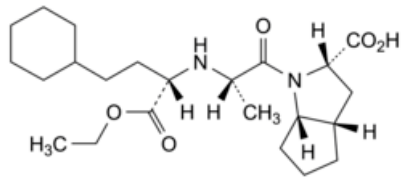
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) E, F, G, H, I, J, K, L, M, N, O.



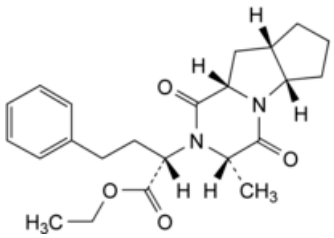
A. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril methyl ester),



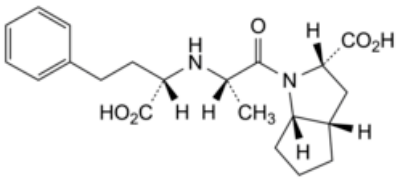
B. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-oxo-4-phenyl-1-[(propan2-yl)oxy]butan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril isopropyl ester),



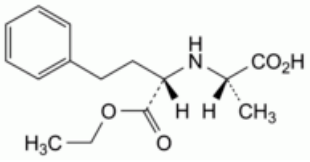
C. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-4-cyclohexyl-1-ethoxy-1oxobutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (hexahydroramipril),



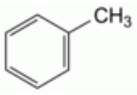
D. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



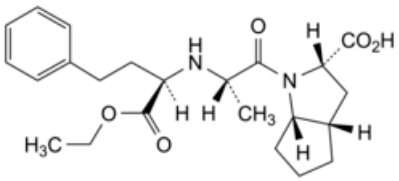
E. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramiprilat),



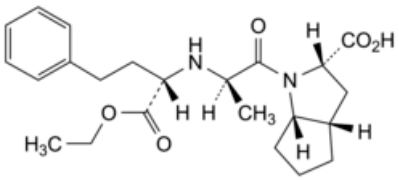
F. (2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoic acid,



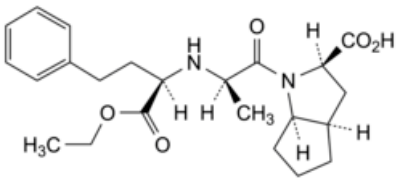
G. methylbenzene (toluene),



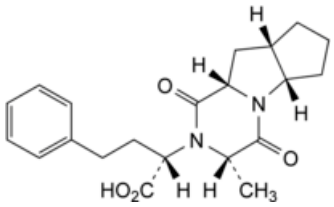
H. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*R*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*R*,*S*,*S*,*S*,*S*)-epimer of ramipril),



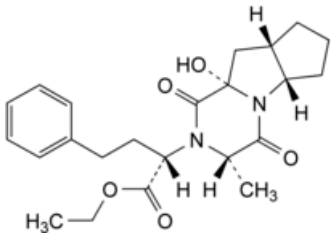
I. (2*S*,3a*S*,6a*S*)-1-[(2*R*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*R*,*S*,*S*,*S*)-epimer of ramipril),



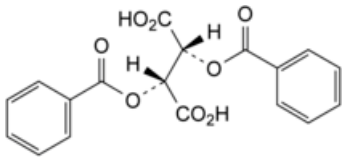
J. (2*R*,3a*R*,6a*R*)-1-[(2*R*)-2-[[(2*R*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (enantiomer of ramipril),



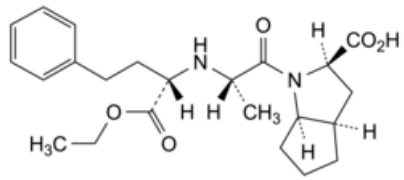
K. (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoic acid (ramiprilate diketopiperazine),



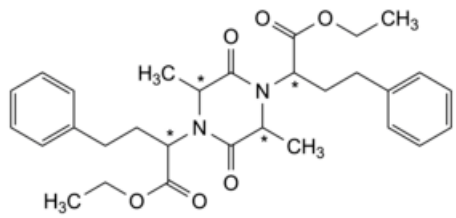
L. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-9a-hydroxy-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



M. (2*R*,3*R*)-2,3-bis(benzoyloxy)butanedioic acid (dibenzoyl tartric acid),



N. (2*R*,3a*R*,6a*R*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*S*,*R*,*R*,*R*)-isomer of ramipril),



O. diethyl (2Ξ,2′Ξ)-2,2′-[(2Ξ,5Ξ)-2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl]bis(4-phenylbutanoate).

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