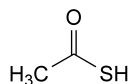


IMPURITIES

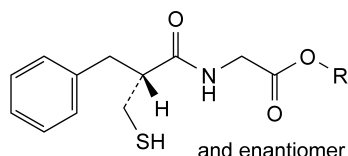
07/2008:1368

Specified impurities: A, C, E, F.

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, D, G, H.

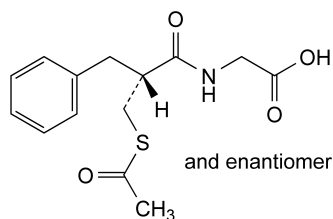


A. ethanethioic acid (thioacetic acid),

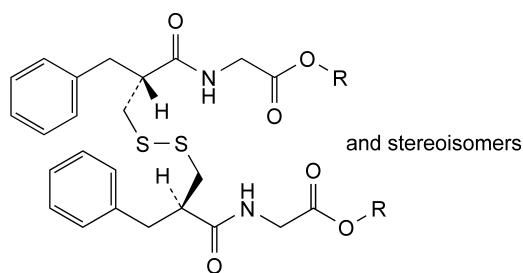


B. R = H: [(2RS)-2-benzyl-3-sulfanylpropanoyl]amino]acetic acid,

G. R = CH₂-C₆H₅: benzyl [(2RS)-2-benzyl-3-sulfanylpropanoyl]amino]acetate,

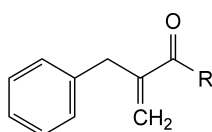


C. (2RS)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]-amino]acetic acid,



D. R = H: 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioic acid,

H. R = CH₂-C₆H₅: dibenzyl 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioate,

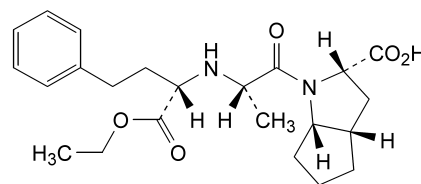


E. R = OH: 2-benzylprop-2-enoic acid (2-benzylacrylic acid),

F. R = NH-CH₂-CO-O-CH₂-C₆H₅: benzyl [(2-benzylprop-2-enoyl)amino]acetate.

RAMIPRIL

Ramiprilum



C₂₃H₃₂N₂O₅
[87333-19-5]

M_r 416.5

DEFINITION

(2S,3aS,6aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]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 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 20.0 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 5 mg of *ramipril impurity A CRS*, 5 mg of *ramipril impurity B CRS*, 5 mg of *ramipril impurity C CRS* and 5 mg of *ramipril impurity D CRS* in 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*: 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 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 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
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.

Relative retention with reference to ramipril (retention time = about 18 min): impurity A = about 0.8; impurity B = about 1.3; impurity G = about 1.4; impurity C = about 1.5; impurity D = about 1.7; impurity O = about 2.4.

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).

Palladium: maximum 20.0 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Dissolve 0.200 g in a mixture of 0.3 volumes of *nitric acid R* and 99.7 volumes of *water R*, and dilute to 100.0 ml with the same mixture of solvents.

Reference solutions. Use solutions containing 0.02 µg, 0.03 µg and 0.05 µg of palladium per millilitre, freshly prepared by dilution of *palladium standard solution (0.5 ppm Pd) R* with a mixture of 0.3 volumes of *nitric acid R* and 99.7 volumes of *water R*.

Modifier solution. Dissolve 0.150 g of *magnesium nitrate R* in a mixture of 0.3 volumes of *nitric acid R* and 99.7 volumes of *water R*, and dilute to 100.0 ml with the same mixture of solvents.

Injection: 20 µl of the test solution and the reference solution, and 10 µl of the modifier solution.

Source: palladium hollow-cathode lamp using a transmission band preferably of 1 nm and a graphite tube.

Wavelength: 247.6 nm.

Loss on drying (2.2.32): maximum 0.2 per cent, determined on 1.000 g by drying in an oven under high vacuum at 60 °C for 4 h.

Sulphated 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 C₂₃H₃₂N₂O₅.

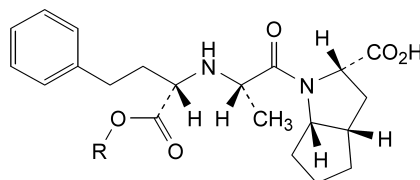
STORAGE

Protected from light.

IMPURITIES

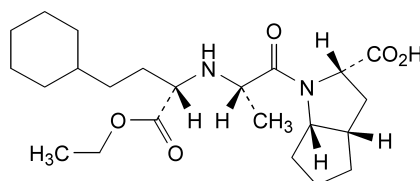
Specified impurities: A, B, C, D.

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.

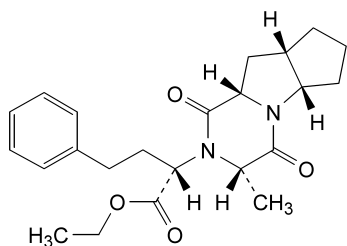


A. R = CH₃: (2S,3aS,6aS)-1-[(2S)-2-[(1S)-1-(methoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (ramipril methyl ester),

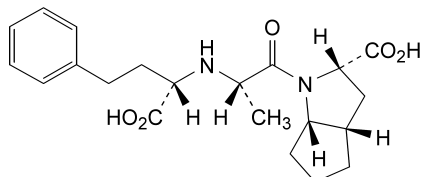
B. R = CH(CH₃)₂: (2S,3aS,6aS)-1-[(2S)-2-[(1S)-1-[(1-methylethoxy)carbonyl]-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (ramipril isopropyl ester),



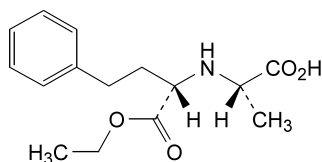
C. (2S,3aS,6aS)-1-[(2S)-2-[(1S)-3-cyclohexyl-1-(ethoxycarbonyl)-propyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (hexahydroramipril),



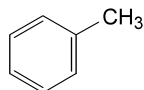
D. ethyl (2*S*)-2-[(3*S*,5*aS*,8*aS*,9*aS*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



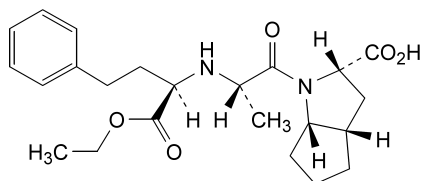
E. (2*S*,3*aS*,6*aS*)-1-[(2*S*)-2-[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril diacid),



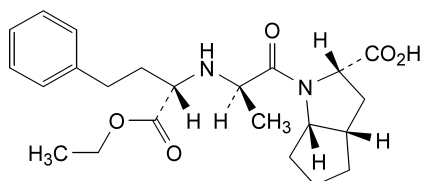
F. (2*S*)-2-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



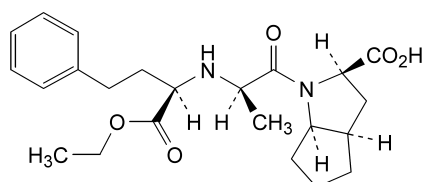
G. methylbenzene (toluene),



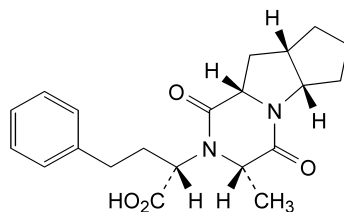
H. (2*S*,3*aS*,6*aS*)-1-[(2*S*)-2-[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*R*,*S*,*S*,*S*,*S*)-epimer of ramipril),



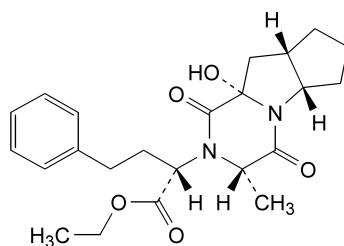
I. (2*S*,3*aS*,6*aS*)-1-[(2*R*)-2-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*R*,*S*,*S*,*S*)-epimer of ramipril),



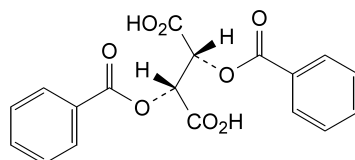
J. (2*R*,3*aR*,6*aR*)-1-[(2*R*)-2-[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (enantiomer of ramipril),



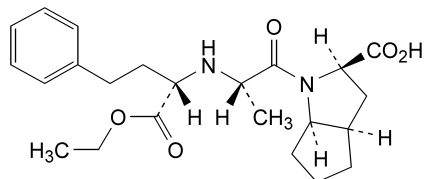
K. (2*S*)-2-[(3*S*,5*aS*,8*aS*,9*aS*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoic acid (ramipril diketopiperazine acid),



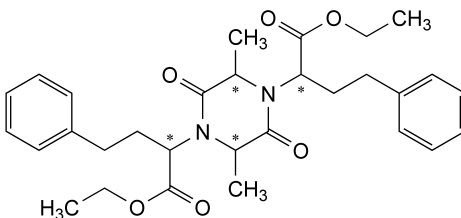
L. ethyl (2*S*)-2-[(3*S*,5*aS*,8*aS*,9*aS*)-9*a*-hydroxy-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



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



N. (2*R*,3*aR*,6*aR*)-1-[(2*S*)-2-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*S*,*R*,*R*,*R*)-isomer of ramipril),



O. diethyl 2,2'-(2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl)bis(4-phenylbutanoate).