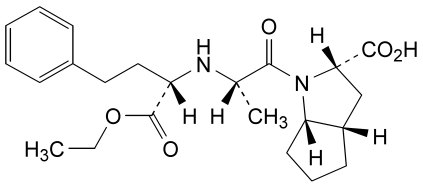
**01/2008:1368**
**corrected 6.0**

# RAMIPRIL

## Ramiprilum



$C_{23}H_{32}N_2O_5$ $M_r$ 416.5
[87333-19-5]

DEFINITION

(2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*S*)-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 R*;
- *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 R*;

| 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 - 40 | 25 | 75 |
| 40 - 45 | 25 → 90 | 75 → 10 |
| 45 - 55 | 90 | 10 |

*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.

*Retention time*: impurity A = about 14 min; ramipril = about 18 min; impurity B = about 22 min; impurity G = about 24 min; impurity C = about 26 min; impurity D = about 28 min.

*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 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 $C_{23}H_{32}N_2O_5$.

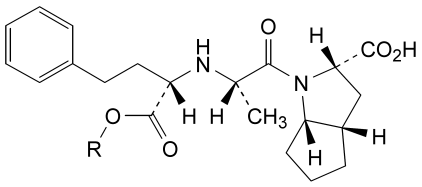
STORAGE

Protected from light.

IMPURITIES

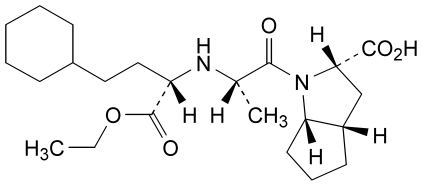
*Specified impurities*: *A, B, C, D.*

*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.*

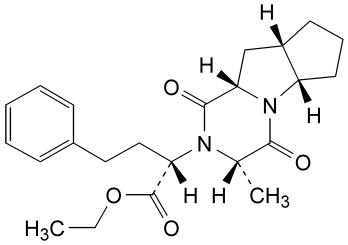


A. R = $CH_3$: (2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*S*)-1-(methoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta-[*b*]pyrrole-2-carboxylic acid (ramipril methyl ester),

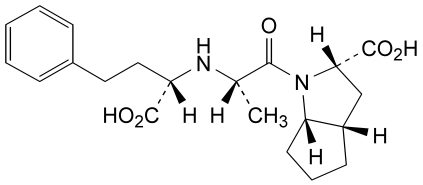
B. R = $CH(CH_3)_2$: (2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*S*)-1-[(1-methylethoxy)carbonyl]-3-phenylpropyl]amino]propanoyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril isopropyl ester),



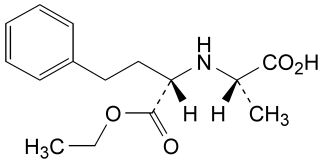
C. (2*S*,3a*S*,6a*S*)1-[(*S*)-2-[[(*S*)-3-cyclohexyl-1-(ethoxycarbonyl)-propyl]amino]propanoyl]octahydrocyclopenta[*b*]-pyrrole-2-carboxylic acid (hexahydroramipril),



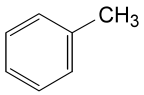
D. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxo-decahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



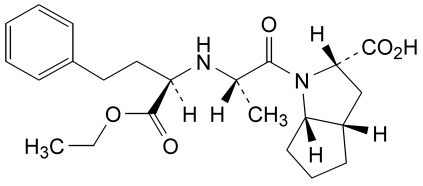
E. (2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*S*)-1-carboxy-3-phenylpropyl]-amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril diacid),



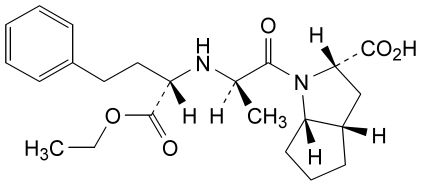
F. (*S*)-2-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-propanoic acid,



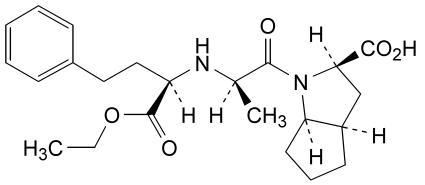
G. toluene,



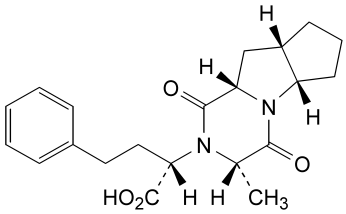
H. (2*S*,3a*S*,6a*S*)-1-[(*R*)-2-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta-[*b*]pyrrole-2-carboxylic acid ((*R*,*S*-*S*,*S*,*S*) isomer of ramipril),



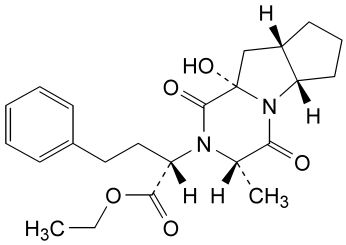
I. (2*S*,3a*S*,6a*S*)-1-[(*S*)-2-[[(*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*R*-*S*,*S*,*S*) isomer of ramipril),



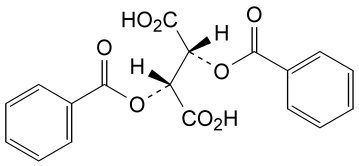
J. (2*R*,3a*R*,6a*R*)-1-[(*R*)-2-[[(*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*R*,*R*-*R*,*R*,*R*) isomer of ramipril),



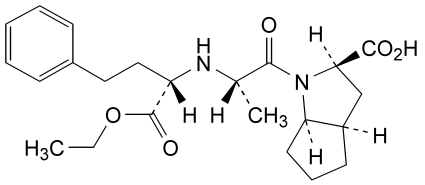
K. (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoic acid (ramipril diketopiperazine acid),



L. ethyl (2S)-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-di(benzoyloxy)butanedioic acid (dibenzoyltartric acid),

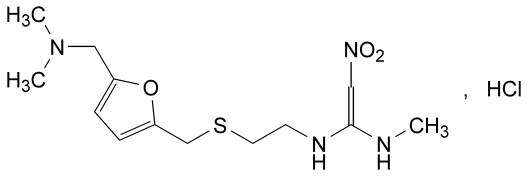


N. (2*R*,3a*R*,6a*R*)-1-[(*S*)-2-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid ((*S*,*S*-*R*,*R*,*R*) isomer of ramipril).

**01/2008:0946**

# RANITIDINE HYDROCHLORIDE

## Ranitidini hydrochloridum



$C_{13}H_{23}ClN_4O_3S$ $M_r$ 350.9
[66357-59-3]

DEFINITION

*N*-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine hydrochloride.

*Content*: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

*Appearance*: white or pale yellow, crystalline powder.

*Solubility*: freely soluble in water, sparingly soluble or slightly soluble in anhydrous ethanol, very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *ranitidine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve 10 mg of the substance to be examined and 10 mg of the reference substance separately in 0.5 ml of *methanol R* in an agate mortar. Evaporate to dryness under a stream of *nitrogen R*. Dry the residues under vacuum for 30 min. Add 3 drops of *liquid paraffin R* to the residues and triturate until the mull shows a milky appearance. Compress the mulls between 2 plates transparent to infrared radiation and record new spectra.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

**Solution S**. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100.0 ml with the same solvent.

**Appearance of solution**. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution $BY_5$ (*2.2.2, Method II*).

**pH** (*2.2.3*): 4.5 to 6.0 for solution S.