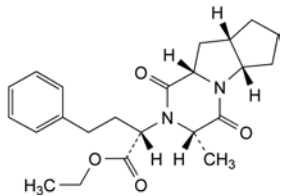
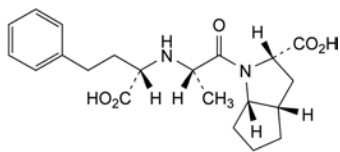


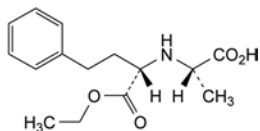
- C. (2S,3aS,6aS)-1-[(2S)-2-[(1S)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (hexahydoramipril),



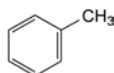
- D. ethyl (2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



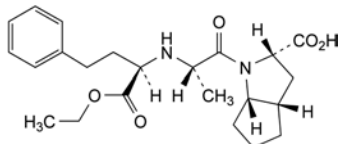
- E. (2S,3aS,6aS)-1-[(2S)-2-[(1S)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (ramipril diacid),



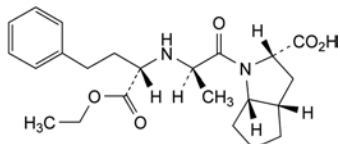
- F. (2S)-2-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



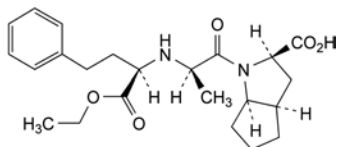
- G. methylbenzene (toluene),



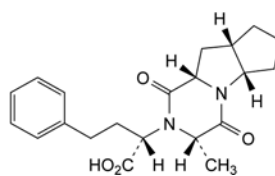
- H. (2S,3aS,6aS)-1-[(2S)-2-[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid ((R,S,S,S,S)-epimer of ramipril),



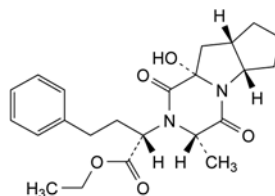
- I. (2S,3aS,6aS)-1-[(2R)-2-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid ((S,R,S,S,S)-epimer of ramipril),



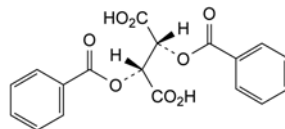
- J. (2R,3aR,6aR)-1-[(2R)-2-[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (enantiomer of ramipril),



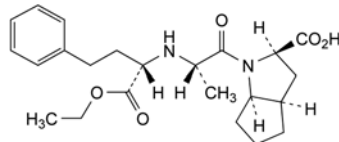
- K. (2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoic acid (ramipril diketopiperazine acid),



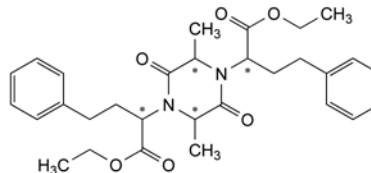
- L. ethyl (2S)-2-[(3S,5aS,8aS,9aS)-9a-hydroxy-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



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



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

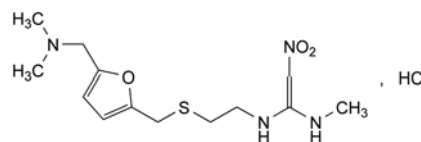


- O. diethyl 2,2'-(2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl)bis(4-phenylbutanoate).

01/2008:0946
corrected 7.0

RANITIDINE HYDROCHLORIDE

Ranitidini hydrochloridum



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

M_r 350.9

DEFINITION

N-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]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 BY₅ (2.2.2, Method II).

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

Related substances. Liquid chromatography (2.2.29).

Buffer solution. Dissolve 6.8 g of *potassium dihydrogen phosphate R* in 950 mL of *water R*. Adjust to pH 7.1 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water R*.

Test solution. Dissolve 13 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a). Dissolve 6.5 mg of *ranitidine for system suitability CRS* (containing impurities A, D and H) in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (c). Dissolve the contents of a vial of *ranitidine impurity J CRS* in 1.0 mL of test solution.

Column:

- size: $l = 0.1$ m, $\varnothing = 4.6$ mm;
- stationary phase: octadecylsilyl amorphous organosilica polymer R (3.5 μ m);
- temperature: 35 °C.

Mobile phase:

- mobile phase A: acetonitrile R, buffer solution (2:98 V/V);
- mobile phase B: acetonitrile R, buffer solution (22:78 V/V);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 μ L of the test solution, reference solutions (a), (b) and (c) and mobile phase A as a blank.

Relative retention with reference to ranitidine (retention time = about 6.8 min): impurity H = about 0.1; impurity G = about 0.2; impurity F = about 0.4; impurity B = about 0.5; impurity C = about 0.6; impurity E = about 0.7; impurity D = about 0.8; impurity J = about 0.9; impurity I = about 1.3; impurity A = about 1.7.

System suitability:

- **resolution:** minimum 1.5 between the peaks due to impurity J and ranitidine in the chromatogram obtained with reference solution (c);
- the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *ranitidine for system suitability CRS*;
- the chromatogram obtained with the blank solution does not show any peak with the same relative retention as the peak due to impurity A in the chromatogram obtained with reference solution (a).

Limits:

- **correction factor:** for the calculation of content, multiply the peak area of impurity J by 2;
- **impurity A:** not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- **impurities B, C, D, E, F, G, H, I, J:** for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- **unspecified impurities:** for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- **sum of impurities other than A:** not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- **disregard limit:** 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the blank.

Heavy metals (2.4.8): maximum 20 ppm.

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (2.2.32): maximum 0.75 per cent, determined on 1.000 g by drying under high vacuum at 60 °C.

Sulfated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.280 g in 35 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 35.09 mg of C₁₃H₂₃ClN₄O₃S.

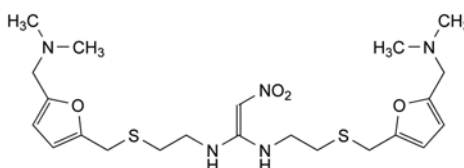
STORAGE

In airtight container, protected from light.

IMPURITIES

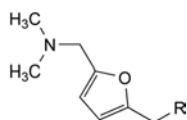
Specified impurities: A, B, C, D, E, F, G, H, I, J.

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*): K.



A. *N,N'*-bis[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,

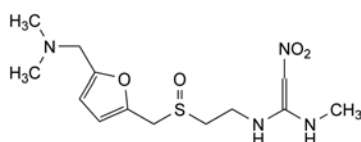
01/2010:1369



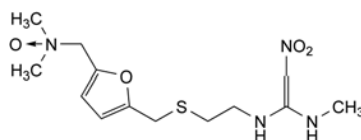
B. R = S-CH₂-CH₂-NH₂: 2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethanamine,

D. R = S-CH₂-CH₂-NH-CO-CH₂-NO₂: *N*-2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,

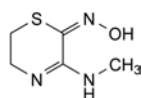
F. R = OH: [5-[(dimethylamino)methyl]furan-2-yl]methanol,



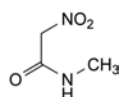
C. *N*-2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N'*-methyl-2-nitroethene-1,1-diamine,



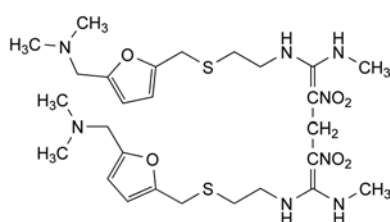
E. *N*-2-[[[5-[(dimethyloxidoamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N'*-methyl-2-nitroethene-1,1-diamine,



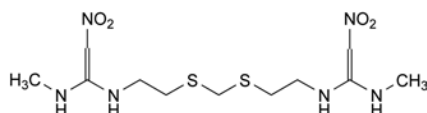
G. 3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one-oxime,



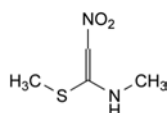
H. *N*-methyl-2-nitroacetamide,



I. 2,2'-methylenebis[*N*-2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-*N'*-methyl-2-nitroethene-1,1-diamine],



J. 1,1'-*N*-[methylenebis(sulfanediylethylene)]bis(*N'*-methyl-2-nitroethene-1,1-diamine),



K. *N*-methyl-1-methylthio-2-nitroethenamine.

RAPESEED OIL, REFINED

Rapae oleum raffinatum

DEFINITION

Fatty oil obtained from the seeds of *Brassica napus* L. and *Brassica campestris* L. by mechanical expression or by extraction. It is then refined. A suitable antioxidant may be added.

CHARACTERS

Appearance: clear, light yellow liquid.

Solubility: practically insoluble in water and in ethanol (96 per cent), miscible with light petroleum (bp: 40-60 °C).

Relative density: about 0.917.

Refractive index: about 1.473.

IDENTIFICATION

Identification of fatty oils by thin-layer chromatography (2.3.2).

Results: the chromatogram obtained is similar to the corresponding chromatogram shown in Figure 2.3.2.-1.

TESTS

Acid value (2.5.1): maximum 0.5, determined on 10.0 g.

Peroxide value (2.5.5, *Method A*): maximum 10.0.

Unsaponifiable matter (2.5.7): maximum 1.5 per cent, determined on 5.0 g.

Alkaline impurities (2.4.19). It complies with the test.

Composition of fatty acids (2.4.22, *Method A*). Use the mixture of calibrating substances in Table 2.4.22.-3.

Composition of the fatty-acid fraction of the oil:

- *palmitic acid*: 2.5 per cent to 6.0 per cent,
- *stearic acid*: maximum 3.0 per cent,
- *oleic acid*: 50.0 per cent to 67.0 per cent,
- *linoleic acid*: 16.0 per cent to 30.0 per cent,
- *linolenic acid*: 6.0 per cent to 14.0 per cent,
- *eicosenoic acid*: maximum 5.0 per cent,
- *erucic acid*: maximum 2.0 per cent.

Water (2.5.32): maximum 0.1 per cent, determined on 1.00 g.

STORAGE

In an airtight, well-filled container, protected from light.

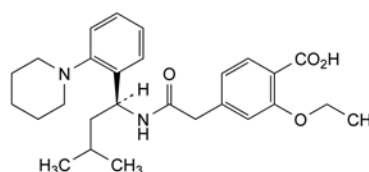
LABELLING

The label states whether the oil is obtained by mechanical expression or by extraction.

01/2008:2135
corrected 6.0

REPAGLINIDE

Repaglinidum



C₂₇H₃₆N₂O₄
[135062-02-1]

*M*_r 452.6