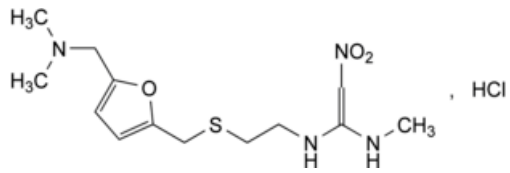
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ranitidine Hydrochloride

General Notices

(Ph. Eur. monograph 0946)



$C_{13}H_{23}ClN_4O_3S$ 350.9 *66357-59-3*

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer disease.

Preparations

Ranitidine Injection

Ranitidine Oral Solution

Ranitidine Tablets

Ranitidine Effervescent Tablets

Ph Eur

DEFINITION

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

Content

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

CHARACTERS

Appearance

White or pale yellow, crystalline powder, hygroscopic.

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.

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 6.8 g of *potassium dihydrogen phosphate R* in 950 mL of *water for chromatography R*. Adjust to pH 7.1 with *strong sodium hydroxide solution R* and dilute to 1000 mL with *water for chromatography 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 impurity A identification CRS* in mobile phase A and dilute to 50 mL with mobile phase A.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (c) Dissolve the contents of a vial of *ranitidine impurity J CRS* in 1 mL of the test solution.

Blank solution Mobile phase A.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl amorphous organosilica polymer for chromatography R* (3.5 µm);

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, buffer solution (2:98 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography 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 µL.

Identification of impurities Use the chromatogram supplied with *ranitidine for impurity A identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity J.

Relative retention With reference to ranitidine (retention time = about 7 min): impurity J = about 0.9; 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 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).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity J by 2.0;

— for each impurity, use the concentration of ranitidine hydrochloride in reference solution (b).

Limits:

— *impurity A*: maximum 0.3 per cent;

— *impurity J*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 0.75 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C at a pressure not exceeding 0.1 kPa.

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 $C_{13}H_{23}ClN_4O_3S$.

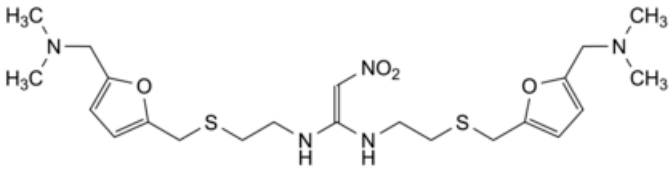
STORAGE

In airtight container, protected from light.

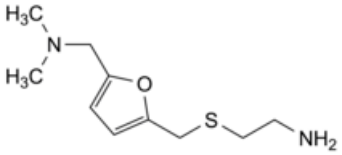
IMPURITIES

Specified impurities A, J.

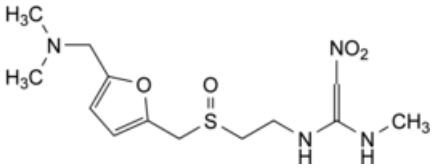
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



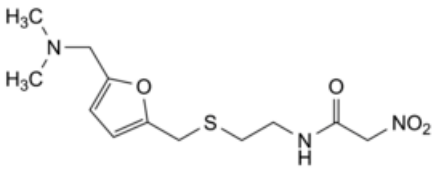
A. *N*,*N*′-bis[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroeth-1-ene-1,1-diamine,



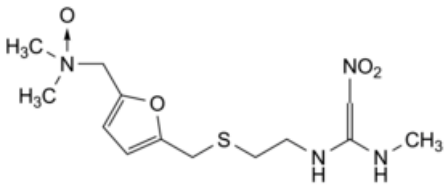
B. 2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethan-1-amine,



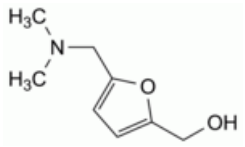
C. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfinyl]ethyl]-*N*′-methyl-2-nitroeth-1-ene-1,1-diamine,



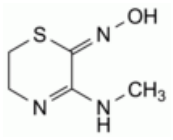
D. *N*-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,



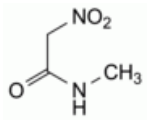
E. [5-[[[2-[[1-(methylamino)-2-nitroeth-1-en-1-yl]amino]ethyl]sulfanyl]methyl]furan-2-yl]-*N*,*N*-dimethylmethanamine *N*-oxide,



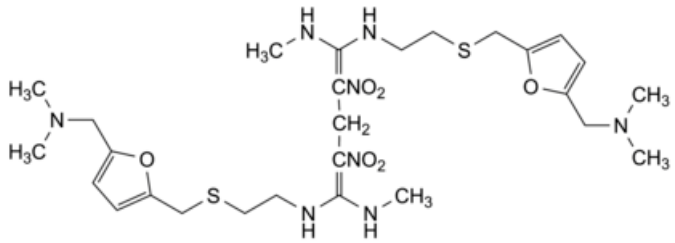
F. [5-[(dimethylamino)methyl]furan-2-yl]methanol,



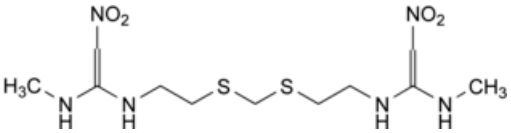
G. [3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-ylidene]hydroxylamine,



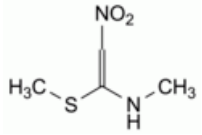
H. *N*-methyl-2-nitroacetamide,



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



J. *N*,*N*″-[methylenebis(sulfanediylethan-2,1-diyl)]bis(*N*′-methyl-2-nitroeth-1-ene-1,1-diamine),



K. *N*-methyl-1-(methylsulfanyl)-2-nitroeth-1-en-1-amine.

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