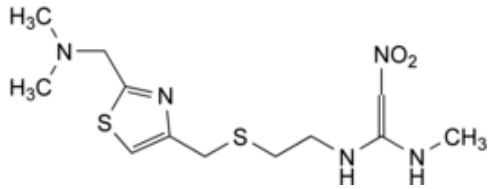
Edition: BP 2025 (Ph. Eur. 11.6 update)

Nizatidine

General Notices

(Ph. Eur. monograph 1453)



$C_{12}H_{21}N_5O_2S_2$ 331.5 *76963-41-2*

Action and use

Histamine H_2 receptor antagonist; treatment of peptic ulcer.

Preparation

Nizatidine Infusion

Ph Eur

DEFINITION

(*EZ*)-*N*-[2-[[[2-[(Dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine.

Content

97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

Almost white or slightly brownish, crystalline powder.

Solubility

Sparingly soluble in water, soluble in methanol.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (2.2.14): 131 °C to 134 °C.
B. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 0.10 g in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of the solution to 100.0 mL with *methanol R*.

Spectral range 220-350 nm.

Absorption maxima At 242 nm and 325 nm.

Absorbance ratio A_{325}/A_{242} = 2.2 to 2.5.

C. Infrared absorption spectrophotometry (2.2.24).

Comparison *nizatidine CRS*.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 50 mg of *nizatidine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 50 mg of *nizatidine CRS* and 50 mg of *ranitidine hydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *water R*, *concentrated ammonia R1*, *2-propanol R*, *ethyl acetate R* (4:8:30:50 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots are clearly visible. Examine in daylight.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_5 (2.2.2, Method II).

Dissolve 0.2 g in a 10 g/L solution of *hydrochloric acid R* and dilute to 20 mL with the same solution.

pH (2.2.3)

8.5 to 10.0.

Dissolve 0.2 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture Mobile phase B, mobile phase A (15:85 *V/V*).

Test solution (a) Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 15.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of *nizatidine CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of the substance to be examined and 0.5 mg of *nizatidine impurity F CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of *2-(dimethylamino)thioacetamide hydrochloride R* (impurity H hydrochloride) in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture. Use 1.0 mL of this solution to dissolve 5 mg of *nizatidine for system suitability CRS* (containing impurities A, B, C, D, G, J and K).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 5.9 g of *ammonium acetate R* in 760 mL of *water R*, add 1 mL of *diethylamine R*, and adjust to pH 7.5 with *acetic acid R*;

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	85	15
3 - 20	85 → 50	15 → 50
20 - 45	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with *nizatidine for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C, D, G, H, J and K; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention With reference to nizatidine (retention time = about 18 min): impurity A = about 0.19; impurity K = about 0.21; impurity H = about 0.5; impurity B = about 0.6; impurity C = about 0.66; impurity J = about 0.7; impurity D = about 0.75; impurity F = about 1.03; impurity G = about 1.5.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to nizatidine and impurity F in the chromatogram obtained with reference solution (c); minimum 1.5 between the peaks due to impurities A and K in the chromatogram obtained with reference solution (d).

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.7; impurity D = 2.3; impurity H = 0.5;

— *impurities A, B, C, D, F, G, H, J, K*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

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

— *total*: not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase B, mobile phase A (35:65 *V/V*).

Injection Test solution (b) and reference solution (b).

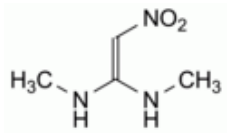
Retention time Nizatidine = 9 min.

Calculate the percentage content of $C_{12}H_{21}N_5O_2S_2$ taking into account the assigned content of *nizatidine CRS*.

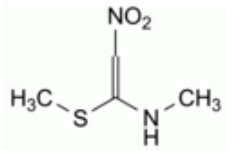
IMPURITIES

Specified impurities *A, B, C, D, F, G, H, J, K.*

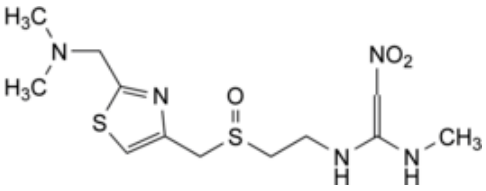
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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, I.*



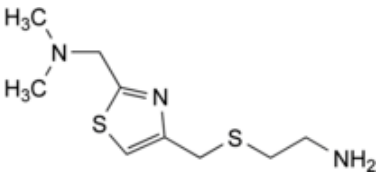
A. *N*,*N*′-dimethyl-2-nitroethene-1,1-diamine,



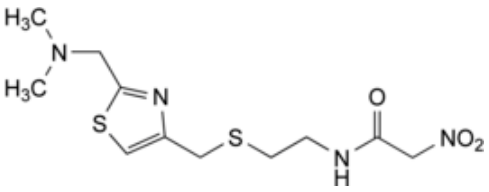
B. (*EZ*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethen-1-amine,



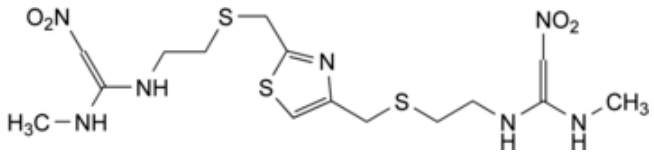
C. (*EZ*)-*N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfinyl]ethyl]-*N*′-methyl-2-nitroethene-1,1-diamine,



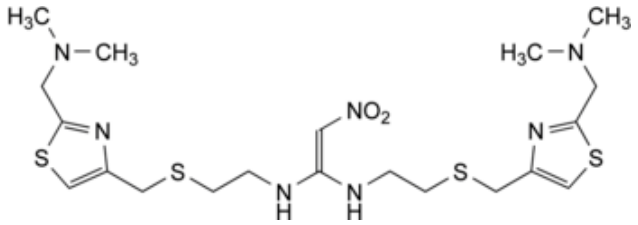
D. 2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethanamine,



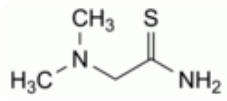
E. *N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-2-nitroacetamide,



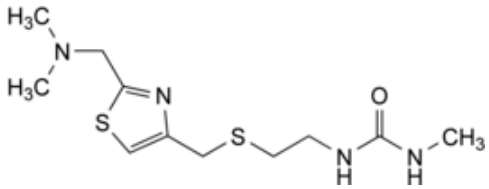
F. (*EZ*)-*N*-methyl-*N*′-[2-[[[4-[[[2-[[(*EZ*)-1-(methylamino)-2-nitroethenyl]amino]ethyl]sulfanyl]methyl]thiazol-2-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,



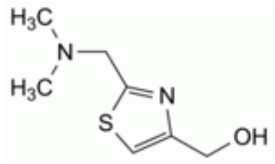
G. *N*,*N*′-bis[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-2-nitroethene-1,1-diamine,



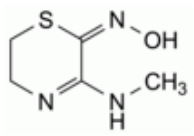
H. 2-(dimethylamino)thioacetamide,



I. *N*-[2-[[[2-[(dimethylamino)methyl]thiazol-4-yl]methyl]sulfanyl]ethyl]-*N*′-methylurea,



J. [2-[(dimethylamino)methyl]thiazol-4-yl]methanol,



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

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