- *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1 per cent);
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent); disregard any peak due to impurity A.

Water (*2.5.12*): 3.5 per cent to 5.0 per cent, determined on 0.300 g.

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

ASSAY

Dissolve 0.300 g in 10 mL of *anhydrous ethanol R* and add 50 mL of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

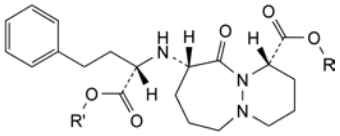
1 mL of *0.1 M sodium hydroxide* is equivalent to 41.75 mg of $C_{22}H_{31}N_3O_5$.

STORAGE

Protected from light.

IMPURITIES

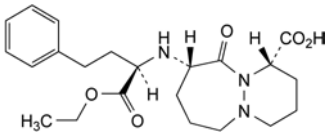
Specified impurities: A, B, C, D.



A. R = $C(CH_3)_3$, R′ = C_2H_5: 1,1-dimethylethyl (1*S*,9*S*)-9-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate,

B. R = R′ = H: (1*S*,9*S*)-9-[[(*S*)-1-carboxy-3-phenylpropyl]-amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid,

C. R = R′ = C_2H_5: ethyl (1*S*,9*S*)-9-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate,

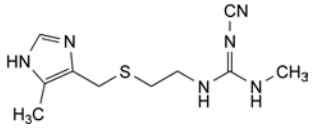


D. (1*S*,9*S*)-9-[[(*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxylic acid.

01/2010:0756
corrected 6.8

CIMETIDINE

Cimetidinum



$C_{10}H_{16}N_6S$ M_r 252.3
[51481-61-9]

DEFINITION

2-Cyano-1-methyl-3-[-2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]ethyl]guanidine.

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

CHARACTERS

Appearance: white or almost white powder.

Solubility: slightly soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute mineral acids.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 139 °C to 144 °C.

If necessary, dissolve the substance to be examined in *2-propanol R*, evaporate to dryness and determine the melting point again.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *cimetidine CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *2-propanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (*2.2.27*).

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

Reference solution. Dissolve 10 mg of *cimetidine CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel GF_{254} plate R*.

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (15:20:65 *V/V/V*).

Application: 5 µL.

Development: over 3/4 of the plate.

Drying: in a current of cold air.

Detection: expose to iodine vapour until maximum contrast has been obtained and examine in ultraviolet light at 254 nm.

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 the reference solution.

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 3.0 g in 12 mL of *1 M hydrochloric acid* and dilute to 20 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 2.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dissolve the contents of a vial of *cimetidine for system suitability CRS* (containing impurities B, C, D, E, G and H) in 1.0 mL of mobile phase A.

Reference solution (c). Dissolve 4 mg of *cimetidine for peak identification CRS* (containing impurity F) in mobile phase A and dilute to 10.0 mL with mobile phase A.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase A: mix 0.4 volumes of *diethylamine R* and 780 volumes of a 1.1 g/L solution of *sodium hexanesulfonate R*; adjust to pH 2.8 with *phosphoric acid R*; add 250 volumes of *methanol R2*;

Mobile phase B: *methanol R2*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	100	0
60 - 65	100 → 90	0 → 10
65 - 120	90	10

Flow rate: 1.1 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 50 µl.

Identification of impurities: use the chromatogram supplied with *cimetidine for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E, G and H; use the chromatogram supplied with *cimetidine for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity F.

Relative retention with reference to cimetidine (retention time = about 18 min): impurity G = about 0.2; impurity E = about 0.4; impurity D = about 1.5; impurity C = about 1.6; impurity B = about 2.0; impurity H = about 2.3; impurity F = about 4.6.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurities D and C.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 2.5; impurity D = 3.3; impurity E = 0.7; impurity G = 0.6.

– *impurities B, C, D, E, F, G, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid* determining the end point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 25.23 mg of $C_{10}H_{16}N_6S$

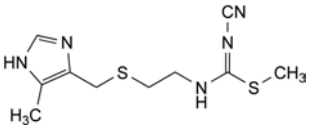
STORAGE

Protected from light.

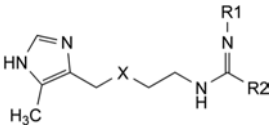
IMPURITIES

Specified impurities: *B, C, D, E, F, G, H.*

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*): *A, I, J.*



A. methyl 3-cyano-1-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]ethyl]carbamimidothioate,

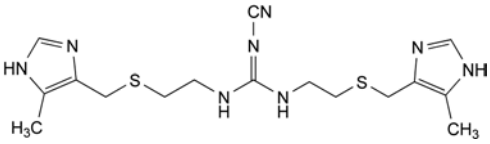


B. R1 = CN, R2 = O-CH_3, X = S: methyl 3-cyano-1-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]ethyl]-carbamimidate,

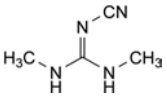
C. R1 = CO-NH_2, R2 = NH-CH_3, X = S: 1-[(methylamino)-[[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]-ethyl]amino]methylidene]urea,

D. R1 = H, R2 = NH-CH_3, X = S: 1-methyl-3-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]ethyl]guanidine,

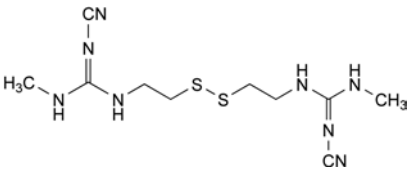
E. R1 = CN, R2 = NH-CH_3, X = SO: 2-cyano-1-methyl-3-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfinyl]-ethyl]guanidine,



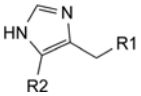
F. 2-cyano-1,3-bis[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]-sulfanyl]ethyl]guanidine,



G. 2-cyano-1,3-dimethylguanidine,



H. 1,1′-(disulfanediyldiethylene)bis(2-cyano-3-methylguanidine),



I. R1 = OH, R2 = C_2H_5: (5-ethyl-1*H*-imidazol-4-yl)methanol,

J. R1 = S-CH_2-CH_2-NH_2, R2 = CH_3: 2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]sulfanyl]ethanamine.