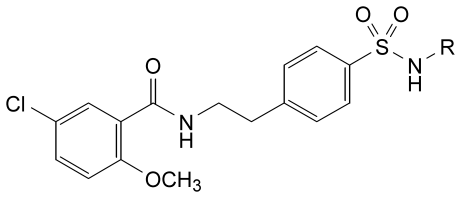
IMPURITIES



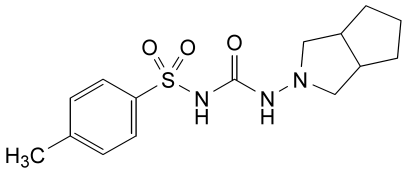
A. R = H: 5-chloro-2-methoxy-*N*-[2-(4-sulphamoylphenyl)ethyl]benzamide,

B. R = CO-OCH_3: methyl [[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulphonyl]carbamate.

01/2008:1524
corrected 6.0

GLICLAZIDE

Gliclazidum



$C_{15}H_{21}N_3O_3S$ M_r 323.4
[21187-98-4]

DEFINITION

1-(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl)sulphonyl]urea.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *gliclazide CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture: *acetonitrile R, water R* (45:55 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in 23 ml of *acetonitrile R* and dilute to 50.0 ml with *water R*.

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

Reference solution (b). Dissolve 5 mg of the substance to be examined and 15 mg of *gliclazide impurity F CRS* in 23 ml of *acetonitrile R* and dilute to 50 ml with *water R*. Dilute 1 ml of this solution to 20 ml with the solvent mixture.

Reference solution (c). Dissolve 10.0 mg of *gliclazide impurity F CRS* in 45 ml of *acetonitrile R* and dilute to 100.0 ml with *water R*. Dilute 1.0 ml of this solution to 100.0 ml with the solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *triethylamine R, trifluoroacetic acid R, acetonitrile R, water R* (0.1:0.1:45:55 *V/V/V/V*).

Flow rate: 0.9 ml/min.

Detection: spectrophotometer at 235 nm.

Injection: 20 µl.

Run time: twice the retention time of gliclazide.

Relative retention with reference to gliclazide (retention time = about 16 min): impurity F = about 0.9.

System suitability: reference solution (b):

– *resolution*: minimum 1.8 between the peaks due to impurity F and gliclazide.

Limits:

– *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 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);

– *sum of impurities other than F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

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

Test solution. Dissolve 0.400 g of the substance to be examined in 2.5 ml of *dimethyl sulphoxide R* and dilute to 10.0 ml with *water R*. Stir for 10 min, store at 4 °C for 30 min and filter.

Reference solution. Dissolve 20.0 mg of *gliclazide impurity B CRS* in *dimethyl sulphoxide R* and dilute to 100.0 ml with the same solvent. To 1.0 ml of the solution, add 12 ml of *dimethyl sulphoxide R* and dilute to 50.0 ml with *water R*. To 1.0 ml of this solution, add 12 ml of *dimethyl sulphoxide R* and dilute to 50.0 ml with *water R*.

Injection: 50 µl.

Retention time: impurity B = about 8 min.

Limit:

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2 ppm).

Heavy metals (*2.4.8*): maximum 10 ppm.

1.5 g complies with test F. Prepare the reference solution using 1.5 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.25 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

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

ASSAY

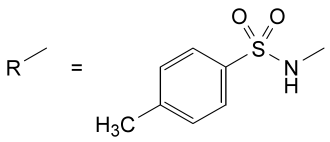
Dissolve 0.250 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 32.34 mg of $C_{15}H_{21}N_3O_3S$.

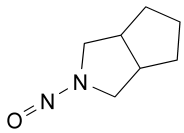
IMPURITIES

Specified impurities: B, F.

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, C, D, E, G.*

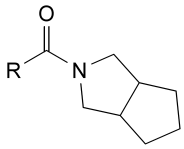


A. R-H: 4-methylbenzenesulphonamide,

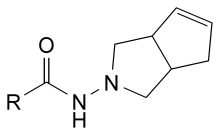


B. 2-nitroso-octahydrocyclopenta[*c*]pyrrole,

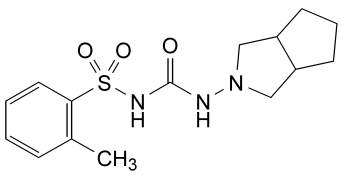
C. R-CO-O-C_2H_5: ethyl [(4-methylphenyl)sulphonyl]-carbamate,



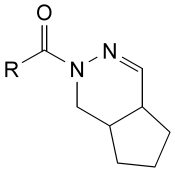
D. *N*-[(4-methylphenyl)sulphonyl]hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-carboxamide,



E. 1-[(4-methylphenyl)sulphonyl]-3-(3,3a,4,6a-tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)urea,



F. 1-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(2-methylphenyl)sulphonyl]urea,

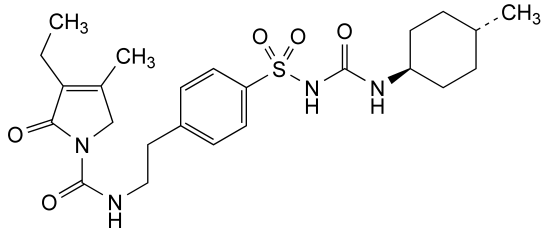


G. *N*-[(4-methylphenyl)sulphonyl]-1,4a,5,6,7,7a-hexahydro-2*H*-cyclopenta[*d*]pyridazine-2-carboxamide.

01/2008:2223

GLIMEPIRIDE

Glimepiridum



$C_{24}H_{34}N_4O_5S$ M_r 490.6
[93479-97-1]

DEFINITION

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl]phenyl]sulphonyl]-3-*trans*-(4-methylcyclohexyl)urea.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, very slightly soluble in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *glimepiride CRS*.

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

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Store the solutions at a temperature not exceeding 12 °C and for not more than 15 h.*

Solvent mixture: *water for chromatography R, acetonitrile for chromatography R* (1:4 *V/V*).

Test solution. Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). Dissolve the contents of a vial of *glimepiride for system suitability CRS* (containing impurities B, C and D) in 2.0 ml of the test solution.

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