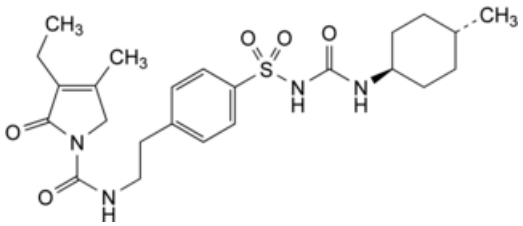
Edition: BP 2025 (Ph. Eur. 11.6 update)

Glimepiride

General Notices

(Ph. Eur. monograph 2223)



$C_{24}H_{34}N_4O_5S$ 490.6 *93479-97-1*

Action and use

Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation

Glimepiride Tablets

Ph Eur

DEFINITION

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-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.

Reference solution (c) Dissolve 20.0 mg of glimepiride CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (4 µm).

Mobile phase Dissolve 0.5 g of sodium dihydrogen phosphate R in 500 mL of water for chromatography R and adjust to pH 2.5 with phosphoric acid R. Add 500 mL of acetonitrile for chromatography R.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Run time 2.5 times the retention time of glimepiride.

Relative retention With reference to glimepiride (retention time = about 17 min): impurity B = about 0.2; impurity C = about 0.3; impurity D = about 1.1.

System suitability Reference solution (a):

— resolution: minimum 4.0 between the peaks due to impurities B and C.

Limits:

— *impurity B*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent),

— *impurity D*: not more than twice 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 the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent),

— *sum of impurities other than B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

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

Impurity A

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

Test solution Dissolve 10.0 mg of the substance to be examined in 5 mL of methylene chloride R and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 0.8 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve 2.0 mg of glimepiride for impurity A identification CRS in 1 mL of methylene chloride R and dilute to 4.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3 mm;

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

Mobile phase anhydrous acetic acid R, 2-propanol R, heptane R (1:100:899 *V/V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 228 nm.

Injection 10 µL.

Run time 1.5 times the retention time of glimepiride.

Identification of impurities Use the chromatogram supplied with glimepiride for impurity A identification CRS and the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention With reference to glimepiride (retention time = about 14 min): impurity A = about 0.9.

System suitability Reference solution (b):

— peak-to-valley ratio: minimum 2.0, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to glimepiride.

Limit:

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent).

Water (2.5.32)

Maximum 0.5 per cent.

Dissolve 0.250 g in dimethylformamide R and dilute to 5.0 mL with the same solvent. Carry out the test on 1.0 mL of solution. Carry out a blank test.

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 modification.

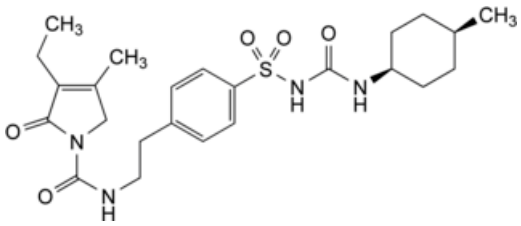
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_{24}H_{34}N_4O_5S$ from the areas of the peaks and the assigned content of glimepiride CRS.

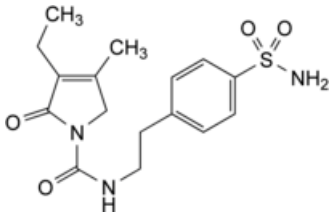
IMPURITIES

Specified impurities A, B, D.

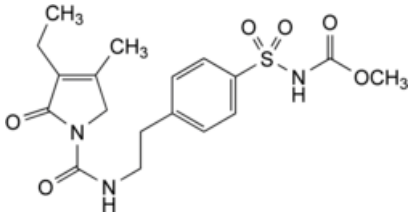
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



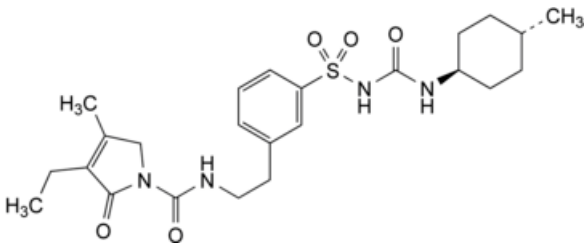
A. 1-[[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*cis*-4-methylcyclohexyl)urea,



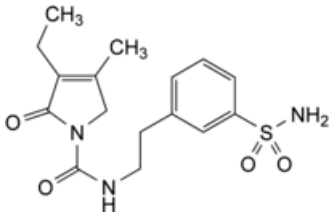
B. 3-ethyl-4-methyl-2-oxo-*N*-[2-(4-sulfamoylphenyl)ethyl]-2,3-dihydro-1*H*-pyrrole-1-carboxamide,



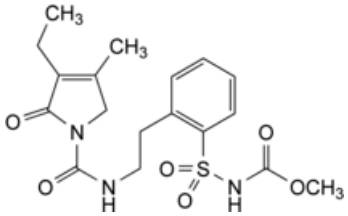
C. methyl [[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]carbamate,



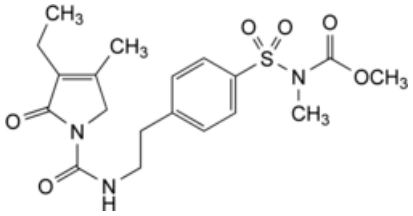
D. 1-[[3-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea,



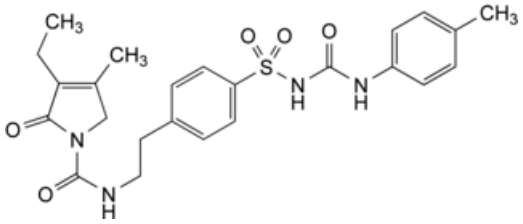
E. 3-ethyl-4-methyl-2-oxo-*N*-[2-(3-sulfamoylphenyl)ethyl]-2,3-dihydro-1*H*-pyrrole-1-carboxamide,



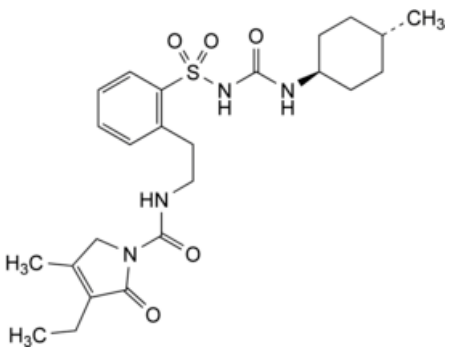
F. methyl [[2-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]carbamate,



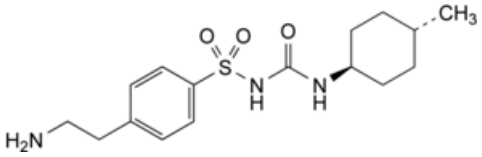
G. methyl [[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]methylcarbamate,



H. 1-[[4-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(4-methylphenyl)urea,



I. 1-[[2-[2-[[(3-ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea,



J. 1-[[4-(2-aminoethyl)phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea.

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