



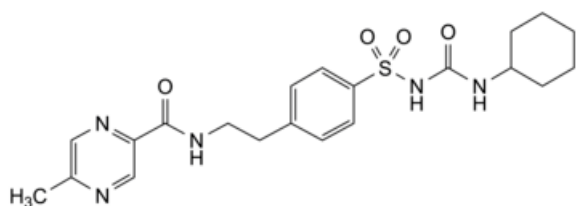
Edition: BP 2025 (Ph. Eur. 11.6 update)

Glipizide



[General Notices](#)

(Ph. Eur. monograph 0906)



$C_{21}H_{27}N_5O_4S$ 445.5 29094-61-9

Action and use

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

Preparation

[Glipizide Tablets](#)

Ph Eur

DEFINITION

N-[2-[4-[(Cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl]-5-methylpyrazine-2-carboxamide.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, very slightly soluble in acetone and in methylene chloride, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A.

Second identification: B.

A. Infrared absorption spectrophotometry ([2.2.24](#)).

Comparison [glipizide CRS](#).

B. Melting point ([2.2.14](#)).

Determination A Determine the melting point of the substance to be examined.

Result A 203 °C to 208 °C.

Determination B Mix equal parts of the substance to be examined and [glipizide CRS](#) and determine the melting point of the mixture.

Result B The absolute difference between the melting point of the mixture and the value obtained in determination A is not greater than 2 °C.

TESTS

Related substances

Liquid chromatography ([2.2.29](#)).

Solvent mixture Mix 40 volumes of [acetonitrile R](#) and 60 volumes of [water R](#) previously adjusted to pH 3.5 with [acetic acid R](#).

Test solution Dissolve 20.0 mg of the substance to be examined in 20.0 mL of [methanol R](#) using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) 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 (b) Dissolve 6.0 mg of [glipizide impurity A CRS](#) in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of [glipizide impurity C CRS](#) in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 100 mL with the solvent mixture.

Reference solution (d) Dissolve 2 mg of [glipizide impurity D CRS](#) in the solvent mixture and dilute to 250 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with reference solution (b).

Column:

— size: $l = 0.25$ m, $\varnothing = 4.6$ mm;

— stationary phase: [base-deactivated end-capped octadecylsilyl silica gel for chromatography R](#) (5 μ m).

Mobile phase:

— mobile phase A: [water for chromatography R](#) adjusted to pH 3.5 with [acetic acid R](#);

— mobile phase B: [acetonitrile for chromatography R](#);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 5	75	25
5 - 12	75 → 65	25 → 35

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
12 - 20	65	35
20 - 25	65 → 50	35 → 50
25 - 30	50	50

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 50 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity D.

Relative retention With reference to glipizide (retention time = about 22 min): impurity A = about 0.25; impurity D = about 0.27; impurity C = about 1.2.

System suitability Reference solution (d):

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

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.7;
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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*: maximum 0.5 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).

Impurity B

Gas chromatography (2.2.28).

Internal standard solution Dissolve 25.0 mg of *decane R* in *methylene chloride R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *methylene chloride R*.

Test solution (a) Dissolve 1.000 g of the substance to be examined in 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of *methylene chloride R*. Use the combined lower layers.

Test solution (b) Dissolve 1.000 g of the substance to be examined in 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of the internal standard solution. Use the combined lower layers.

Reference solution Dissolve 10.0 mg of *cyclohexylamine R* (impurity B) in a 17.5 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. To 1.0 mL of this solution add 50 mL of a 12 g/L solution of *sodium hydroxide R* and shake with 2 quantities, each of 5.0 mL, of the internal standard solution. Use the combined lower layers.

Column:

- *material*: fused silica;
- *size*: $l = 25$ m, $\varnothing = 0.32$ mm;
- *stationary phase*: *phenyl(5)methyl(95)polysiloxane R* (film thickness 0.5 µm).

Carrier gas *helium for chromatography R*.

Flow rate 1.8 mL/min.

Split ratio 1:11.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 4	40
	4 - 20	40 → 200
	20 - 25	200
Injection port		250
Detector		270

Detection Flame ionisation.

Injection 1 µL.

Elution order Impurity B, decane.

System suitability:

- [resolution](#): minimum 7 between the peaks due to impurity B and the internal standard in the chromatogram obtained with the reference solution;
- there is no peak with the same retention time as that of the internal standard in the chromatogram obtained with test solution (a).

Calculate the ratio (*R*) of the area of the peak due to impurity B to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with test solution (b), calculate the ratio of the area of any peak due to impurity B to the area of the peak due to the internal standard.

Limit:

- impurity B: not more than *R* (100 ppm).

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

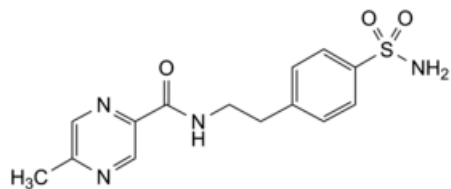
Dissolve 0.400 g in 50 mL of [dimethylformamide R](#). Add 0.2 mL of [quinaldine red solution R](#). Titrate with [0.1 M lithium methoxide](#) until the colour changes from red to colourless.

1 mL of [0.1 M lithium methoxide](#) is equivalent to 44.55 mg of C₂₁H₂₇N₅O₄S.

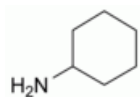
IMPURITIES

Specified impurities A, B, C.

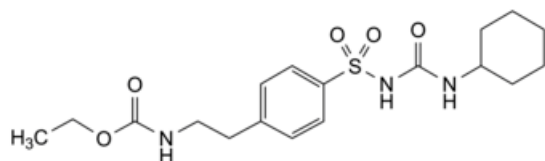
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph [Substances for pharmaceutical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



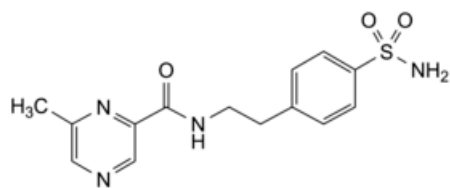
A. 5-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide,



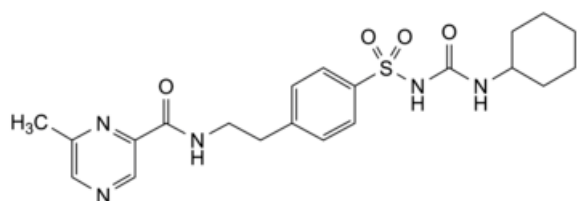
B. cyclohexanamine (cyclohexylamine),



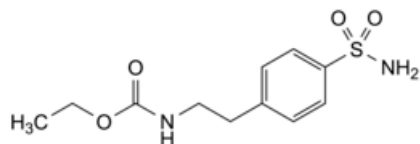
C. ethyl 2-[4-[(cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl carbamate,



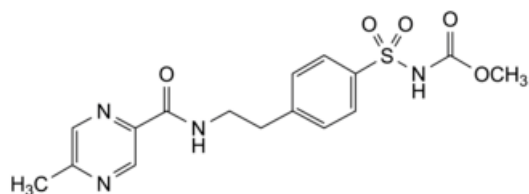
D. 6-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide,



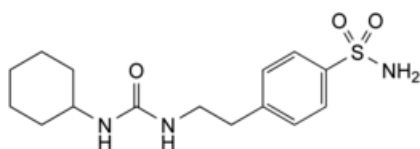
E. *N*-[2-[4-[(cyclohexylcarbamoyl)sulfamoyl]phenyl]ethyl]-6-methylpyrazine-2-carboxamide,



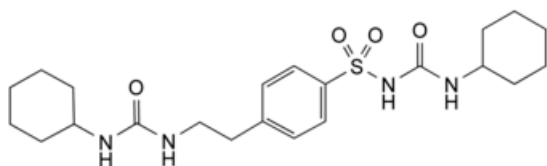
F. ethyl 2-(4-sulfamoylphenyl)ethyl carbamate,



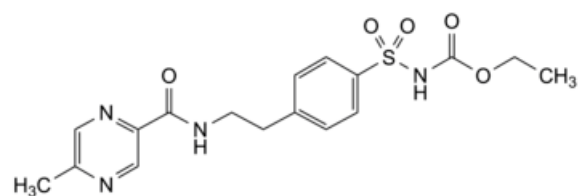
G. methyl [4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene-1-sulfonyl]carbamate,



H. 4-[2-[(cyclohexylcarbamoyl)amino]ethyl]benzene-1-sulfonamide,



I. N-(cyclohexylcarbamoyl)-4-[2-[(cyclohexylcarbamoyl)amino]ethyl]benzene-1-sulfonamide,



J. ethyl [4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene-1-sulfonyl]carbamate.

Ph Eur