World Health Organization

GLICLAZIDE

(GLICLAZIDUM)

Draft proposal for inclusion in *The International Pharmacopoeia*

(30 June 2025)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int, nsp@who.int).
Comments should be submitted through the online platform on or by **29 August 2025**. Please note that only comments received by this deadline will be considered for the preparation of this document.
Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation".

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT

GLICLAZIDE

(GLICLAZIDUM)

Description	Date
First draft prepared.	March 2025
Discussion at the informal Consultation on Quality Control and Pharmacopoeial Specifications of Medicines	April 2025
Draft revision sent out for public consultation	August – September 2025
Draft revision presented at the 59th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.	October 2025
Further follow-up action as required.	

*[**Note from the Secretariat**. The monograph on Gliclazide is proposed for inclusion in* The International Pharmacopoeia.

The monograph is based on information found in other pharmacopoeias, in the scientific literature and on laboratory investigations.

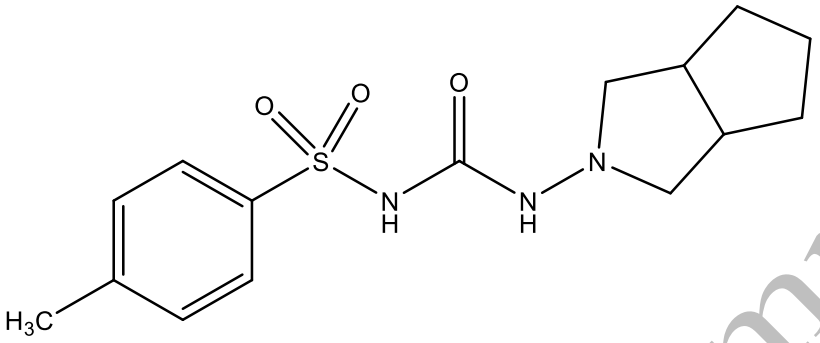
Draft monographs are subject to change.]

GLICLAZIDE (GLICLAZIDUM)

Molecular formula. $C_{15}H_{21}N_3O_3S$

Relative molecular mass. 323.4

Graphic formula.



Chemical name. *N*-[(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]-4-methylbenzene-1-sulfonamide

CAS Registry No. 21187-98-4.

Description. A white or almost white powder.

Solubility. Practically insoluble in water R; freely soluble in dichloromethane R, sparingly soluble in acetone R, slightly soluble in ethanol (~750 g/l) TS.

Category. Antidiabetic drug.

Storage. Gliclazide should be kept in a well-closed container.

Additional information. Gliclazide may show polymorphism.

Requirements

Definition. Gliclazide contains not less than 99.0% and not more than 101.0% of $C_{15}H_{21}N_3O_3S$, calculated with reference to the dried substance.

Identity tests

- Either test A alone, or any two of tests B, C or D may be applied.

A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from gliclazide RS or with the reference spectrum of gliclazide.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and gliclazide RS in a small amount of dichloromethane R and evaporating to dryness. The infrared absorption spectrum of the test substance is concordant with the spectrum obtained from gliclazide RS.

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions and solution (2) given under "Related substances". For solution (3), prepare a solution containing 0.01 mg/mL gliclazide RS in the given diluent.

The retention time of the principal peak in the chromatogram obtained with solution (2) corresponds to the retention time of the peak due to gliclazide in the chromatogram obtained with solution (3).

C. The absorption spectrum (*1.6 Spectrophotometry in the visible and ultraviolet regions*) of a 0.01 mg per mL solution of the test substance prepared in a mixture of 45 volumes of acetonitrile R and 55 volumes of water R, when observed between 200 nm and 300 nm, exhibits a minimum at about 213 nm and a maximum at about 229 nm.

Alternatively, and in combination with identity test B, where a diode-array

detector is available, record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 210 nm to 340 nm. The UV spectrum of the principal peak in the chromatogram obtained with solution (2) corresponds to the UV spectrum of the peak due to gliclazide, obtained with solution (3).

D. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a freshly prepared mixture of toluene R and ethyl acetate R (1:1 *V*/*V*) as the mobile phase.

Apply separately to the plate 2 µL of each of the following 2 solutions in dichloromethane R containing (A) 0.4 mg of the test substance per mL and (B) 0.4 mg of gliclazide RS per mL.

Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air. Examine the plate and under ultraviolet light (254 nm).

The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to gliclazide in the chromatogram obtained with solution (B).

Heavy metals. Use 1.000 g for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

Sulfated ash *(2.3)*. Not more than 1.0 mg/g, determined on 1.000 g.

Loss on drying. Dry at 105 °C for 2 hours; it loses not more than 2.5 mg/g.

Related substances. Prepare the solutions immediately before use. Carry out the test as described under *1.14.1 Chromatography*, High-pressure liquid chromatography, using a stainless steel column (4 mm x 25 cm) packed with particles of silica gel,

the surface of which has been modified with chemically-bonded octylsilyl groups[1] (4 µm).

As the mobile phase, use a mixture of 0.1 volume of triethylamine R, 0.1 volume of trifluoroacetic acid R, 45 volumes of acetonitrile R and 55 volumes of water R.

Operate with a flow rate of 0.9 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 235 nm. Maintain the autosampler temperature at 4 °C.

Prepare the following solutions. Use as a diluent a mixture of 45 volumes of acetonitrile R and 55 volumes of water R.

For solution (1), dissolve 50.0 mg of the test substance in 23 mL of acetonitrile R and dilute to 50.0 mL with water R.

For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with the diluent.

For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL with the same solvent.

For solution (4), dissolve 5 mg of the test substance and 15 mg of gliclazide impurity F RS in 23 mL of acetonitrile R and dilute to 50.0 mL with water R. Dilute 1 mL of the solution to the 20 mL with the diluent.

For solution (5), dissolve 15.0 mg gliclazide impurity F RS 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 diluent.

Inject 20 µL each of solutions (1), (2), (3), (4) and (5). Record the chromatogram for about 2 times the retention time of gliclazide (retention time about 16 minutes).

[1]A Superspher 60 RP-8 LiChroCART column has been found suitable.

Use the chromatogram obtained with solution (4) and (5) to identify the peak due to gliclazide impurity F.

The impurities are eluted, if present, at the following relative retentions with reference to gliclazide: impurity F about 0.9.

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between impurity F and gliclazide is at least 1.8. Also, the test is not valid unless in the chromatogram obtained with solution (3) the peak due to gliclazide is detected with a signal-to-noise ration of at least 10.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity F is not greater than the area of the peak due to gliclazide impurity F in the chromatogram obtained with solution (5) (0.15 %);
- the area of any other impurity peak is not greater than 0.1 times the area of the peak due to gliclazide in the chromatogram obtained with solution (2) (0.10 %).
- The sum of the areas of all impurity peaks, excluding the area of any peak corresponding to impurity F, is not greater than 0.2 times the area of the peak due to gliclazide in the chromatogram obtained with solution (2) (0.2%). Disregard any peaks with an area of less than the area of the peak due to gliclazide in the chromatogram obtained with solution (3) (0.05%).

Impurity B. Carry out the test as described under *1.14.1 Chromatography*, Liquid chromatography, using the conditions given under "Related substances", with the following modifications.

For solution (1), dissolve 0.400 g of the test substance in 2.5 mL of dimethyl sulfoxide R and dilute to 10.0 mL using water R. Stir this solution for 10 min, store at 4 °C for 30 min and filter.

For solution (2), dissolve 20.0 mg of gliclazide impurity B RS in dimethyl sulfoxide R and dilute to 100.0 mL with the same solvent. To 1.0 mL of the solution, add 12 mL of dimethyl sulfoxide R and dilute to 50.0 mL with water R. To 1.0 mL of this solution, add 12 mL of dimethyl sulfoxide R and dilute to 50.0 mL with water R.

Inject 50 µL each of solutions (1) and (2).

Use the chromatogram obtained with solution (2) to identify the peak due to gliclazide impurity B (retention time about 7 minutes).

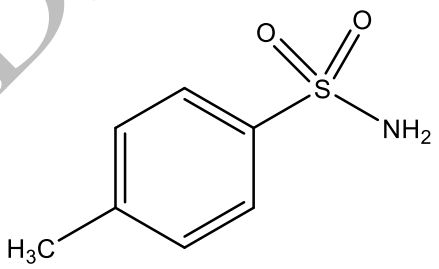
The test is not valid unless in the chromatogram obtained with solution (2) the peak due to gliclazide impurity B is detected with a signal-to-noise ration of at least 10.

In the chromatogram obtained with solution (1):

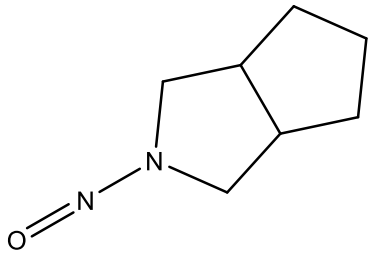
- the area of any peak corresponding to impurity B is not greater than the area of the peak due to gliclazide impurity B in the chromatogram obtained with solution (2) (2 ppm).

Assay. Dissolve 0.250 g in 50 mL of anhydrous acetic acid R. Titrate with perchloric acid (0.1 mol/L) VS determining the endpoint potentiometrically, as described under *2.6 Non-aqueous titration*, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 32.34 mg of $C_{15}H_{21}N_3O_3S$.

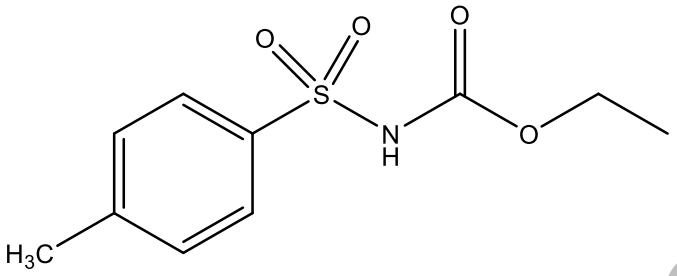
Impurities



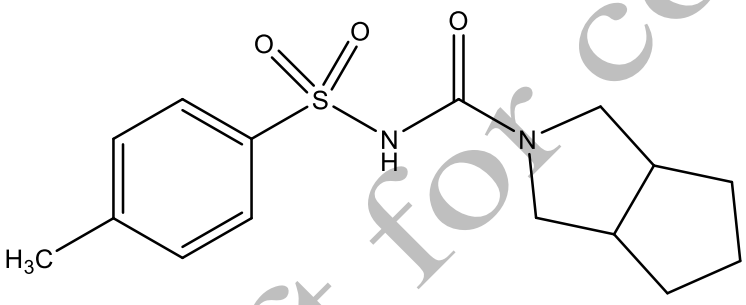
A. 4-methylbenzene-1-sulfonamide.



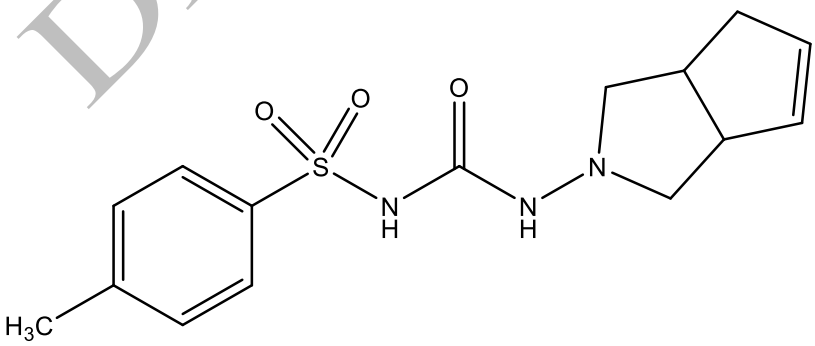
B. 2-nitrosooctahydrocyclopenta[*c*]pyrrole.



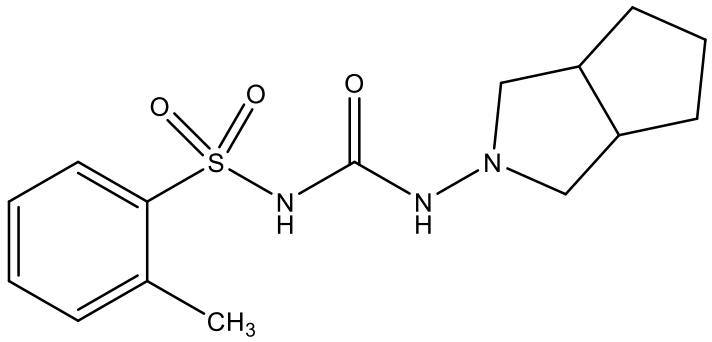
C. ethyl (4-methylbenzene-1-sulfonyl)carbamate.



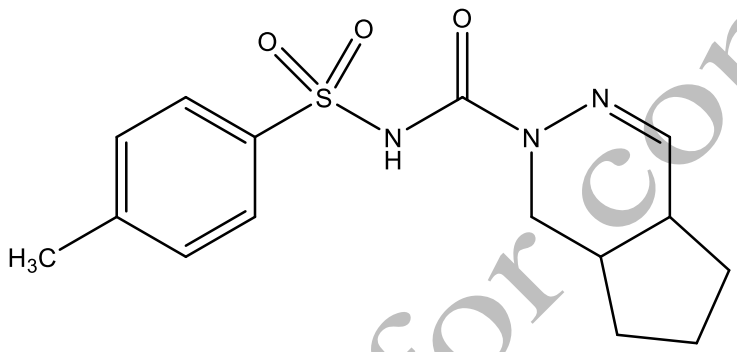
D. *N*-(4-methylbenzene-1-sulfonyl)hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-carboxamide.



E. 4-methyl-*N*-[(3,3a,4,6a-tetrahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]benzene-sulfonamide.



F. 2-methyl-*N*-[(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)carbamoyl]benzene-1-sulfonamide.



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

Reference substances to be established.

Gliclazide impurity F RS

- *It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.*

Gliclazide impurity B RS

- *It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.*

Gliclazide RS

- *ICRS to be established*

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