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### **GLICLAZIDE**

(GLICLAZIDUM)

# Draft proposal for inclusion in The International Pharmacopoeia

(30 June 2025)

# 6 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 (<a href="mailto:schmidth@who.int">schmidth@who.int</a>), with a copy to Ms Sinéad Jones (<a href="mailto:jonessi@who.int">jonessi@who.int</a>), msp@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.

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT

#### 35 GLICLAZIDE

### (GLICLAZIDUM)

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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 59 <sup>th</sup> meeting of the Expert Committee on Specifications for Pharmaceutical Preparations.	October 2025
Further follow-up action as required.	

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- 40 [Note from the Secretariat. The monograph on Gliclazide is proposed for inclusion in
- 41 The International Pharmacopoeia.
- 42 The monograph is based on information found in other pharmacopoeias, in the
- 43 scientific literature and on laboratory investigations.
- 44 Draft monographs are subject to change.]

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# GLICLAZIDE (GLICLAZIDUM)

- 48 Molecular formula. C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S
- 49 Relative molecular mass. 323.4
- 50 Graphic formula.

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- Chemical name. N-[(Hexahydrocyclopenta[c]pyrrol-2(1H)-yl)carbamoyl]-4-
- 53 methylbenzene-1-sulfonamide
- 54 **CAS Registry No.** 21187-98-4.
- **Description.** A white or almost white powder.
- 56 Solubility. Practically insoluble in water R; freely soluble in dichloromethane R,
- sparingly soluble in acetone R, slightly soluble in ethanol (~750 g/l) TS.
- 58 Category. Antidiabetic drug.
- 59 **Storage.** Gliclazide should be kept in a well-closed container.
- 60 **Additional information.** Gliclazide may show polymorphism.
- 61 Requirements

- **Definition.** Gliclazide contains not less than 99.0% and not more than 101.0% of
- 63 C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S, calculated with reference to the dried substance.

## 64 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
- 73 gliclazide RS.
- B. Carry out the test as described under <u>1.14.1 Chromatography</u>, High-performance
- 75 liquid chromatography, using the conditions and solution (2) given under "Related
- substances". For solution (3), prepare a solution containing 0.01 mg/mL gliclazide
- 77 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).
- 81 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)
- orresponds to the UV spectrum of the peak due to gliclazide, obtained with
- 91 solution (3).
- 92 D. Carry out the test as described under <u>1.14.1 Chromatography</u>, 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
- 97 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
- 103 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  $10 \mu g/g$ .
- 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.
- 109 **Related substances.** Prepare the solutions immediately before use. Carry out the test
- as described under <u>1.14.1 Chromatography</u>, 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<sup>1</sup>
- 113  $(4 \mu m)$ .
- 114 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.
- 119 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
- FRS 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).

<sup>&</sup>lt;sup>1</sup>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)
- 147 (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%).
- 153 **Impurity B.** Carry out the test as described under 1.14.1 Chromatography, Liquid
- 154 chromatography, using the conditions given under "Related substances", with the
- 155 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  $\mu$ L 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**

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178 A. 4-methylbenzene-1-sulfonamide.

B. 2-nitrosooctahydrocyclopenta[c]pyrrole.

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

184 D. N-(4-methylbenzene-1-sulfonyl)hexahydrocyclopenta[c]pyrrol-2(1H)185 carboxamide.

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187 E. 4-methyl-N-[(3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-

yl)carbamoyl]benzene-sulfonamide.

190 F. 2-methyl-N-[(hexahydrocyclopenta[c]pyrrol-2(1H)-

191 yl)carbamoyl]benzene-1-sulfonamide.

193 G. N-[(4-methylbenzene-1-sulfonyl)-1,4a,5,6,7,7a-hexahydro-2H-

194 cyclopenta[d]pyridazine-2-carboxamide.

196 Reference substances to be established.

197 *Gliclazide impurity F RS* 

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

200 Gliclazide impurity B RS

201 202	• It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.
203	Gliclazide RS
204	• ICRS to be established
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