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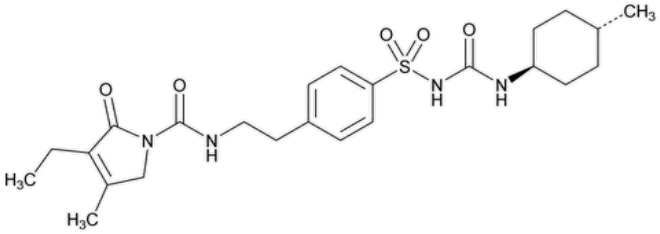
Glimepiride



$C_{24}H_{34}N_4O_5S$ 490.62

1*H*-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-*N*-[2-[4-[[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-, *trans*-;

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea CAS RN®: 93479-97-1; UNII: 6KY687524K.

DEFINITION

Glimepiride contains NLT 98.0% and NMT 102.0% of glimepiride ($C_{24}H_{34}N_4O_5S$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) [Note—Methods described in ⟨197K⟩ or ⟨197A⟩ may be used.]

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Mobile phase: Dissolve 0.5 g of monobasic sodium phosphate in 500 mL of water. Adjust with phosphoric acid to a pH of 2.1–2.7, and add 500 mL of acetonitrile.

Diluent: Acetonitrile and water (4:1)

Standard solution: 0.2 mg/mL of USP Glimepiride RS in *Diluent*

System suitability stock solution: 0.1 mg/mL each of USP Glimepiride Related Compound B RS, USP Glimepiride Related Compound C RS, and USP Glimepiride Related Compound D RS in *Diluent*

System suitability solution: Dilute 1 mL of the *System suitability stock solution* with the *Standard solution* to 50 mL.

Sample solution: 0.2 mg/mL of Glimepiride in *Diluent*. [Note—Keep the *Sample solution* at a temperature not exceeding 12°, and store it no longer than 15 h.]

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 228 nm

Column: 4-mm × 25-cm or 4.6-mm × 25-cm; 4- or 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[Note—See *Table 1* for relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between glimepiride related compound B and glimepiride related compound C, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of glimepiride ($C_{24}H_{34}N_4O_5S$) in the portion of Glimepiride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Glimepiride RS in the *Standard solution* (mg/mL)

C_U = concentration of Glimepiride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.2%
- **Limit of *cis*-Isomer (Glimepiride Related Compound A)**

Mobile phase: Transfer 100 mL of isopropyl alcohol to a 1-L volumetric flask, add 1 mL of glacial acetic acid, and dilute with hexane to volume.

System suitability stock solution: Dissolve 1 mg of USP Glimepiride Related Compound A RS in 1 mL of methylene chloride. Add 3 mL of *Mobile phase*, and mix.

System suitability solution: Transfer 10 mg of USP Glimepiride RS into a 20-mL volumetric flask, dissolve in 5 mL of methylene chloride, and dilute with *Mobile phase* to volume. Transfer 5 mL of this solution to a separate flask, add 50 µL of the *System suitability stock solution*, and mix.

Sample solution: Transfer 10 mg of Glimepiride into a 20-mL volumetric flask, dissolve in 5 mL of methylene chloride, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 228 nm

Column: 3-mm × 15-cm; 5-µm packing L20

[Note—The analyses could also be performed with 4.6-mm × 15-cm, 4.6-mm × 25-cm, 4-mm × 12.5-cm, or 4-mm × 25-cm columns containing packing L20. It is recommended that the flow rate be adjusted to about 1.1 mL/min for a 4.6-mm column and to about 0.8 mL/min for a 4.0-mm column.]

Flow rate: 0.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for glimepiride *cis*-isomer and glimepiride are 0.9 and 1.0, respectively.]

Suitability requirements

Signal-to-noise ratio: NLT 15 for the glimepiride *cis*-isomer peak

Peak-to-valley ratio: NLT 2.0 for glimepiride *cis*-isomer and glimepiride

Analysis

Sample: *Sample solution*

Calculate the percentage of glimepiride *cis*-isomer in the portion of Glimepiride taken:

$$\text{Result} = r_{cis}/(r_{cis} + r_G) \times 100$$

r_{cis} = peak area of glimepiride *cis*-isomer from the *Sample solution*

r_G = peak area of glimepiride from the *Sample solution*

Acceptance criteria: NMT 0.8%

- **Organic Impurities**

Mobile phase, Diluent, Standard solution, System suitability solution, Sample solution, and **System suitability:** Proceed as directed in the *Assay*.

Diluted sample solution 1: Dilute 5.0 mL of the *Sample solution* with *Diluent* to 100.0 mL. Dilute 5.0 mL of the solution obtained with *Diluent* to 50.0 mL. This solution contains about 0.001 mg/mL of glimepiride.

Diluted sample solution 2: Dilute 1.0 mL of *Diluted sample solution 1* with *Diluent* to 10.0 mL.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Run time*.

Run time: 2.5 times the retention time of the glimepiride peak

Analysis

Samples: *Sample solution*, *Diluted sample solution 1*, and *Diluted sample solution 2*

Calculate the percentage of each impurity in the portion of Glimepiride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of glimepiride from *Diluted sample solution 1*

C_S = concentration of Glimepiride in *Diluted sample solution 1* (mg/mL)

C_U = concentration of Glimepiride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*. Disregard any peak with an area less than that of the glimepiride peak from *Diluted sample solution 2*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Glimepiride sulfonamide (glimepiride related compound B)	0.2	0.4
Glimepiride urethane (glimepiride related compound C)	0.3	0.1
Glimepiride	1.0	—
Glimepiride 3-isomer (glimepiride related compound D)	1.1	0.2
Any individual unspecified impurity	—	0.1
Total impurities, excluding glimepiride related compound B	—	0.5

SPECIFIC TESTS

• **Water Determination** ⟨921⟩, *Method I, Method Ic*

Sample solution: Dissolve 0.25 g of Glimepiride in dimethylformamide previously dried over a 2-mm molecular sieve with 0.4-nm pore size, and dilute with the same solvent to 5.0 mL.

Analysis: Use 1.0 mL of the *Sample solution*. Perform a blank determination, using 1.0 mL of the solvent.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Store in well-closed containers, at a temperature not exceeding 25°.

• **USP Reference Standards** ⟨11⟩

USP Glimepiride RS

USP Glimepiride Related Compound A RS

Glimepiride *cis*-isomer;
1-[[*p*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*cis*-4-methylcyclohexyl)urea.
$C_{24}H_{34}N_4O_5S$ 490.62

USP Glimepiride Related Compound B RS

Glimepiride sulfonamide;
3-Ethyl-4-methyl-2-oxo-*N*-(4-sulfamoylphenethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxamide.
$C_{16}H_{21}N_3O_4S$ 351.42

USP Glimepiride Related Compound C RS

Glimepiride urethane;
Methyl ({4-[2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamido)ethyl]phenyl}sulfonyl)carbamate.
$C_{18}H_{23}N_3O_6S$ 409.46

USP Glimepiride Related Compound D RS

Glimepiride 3-isomer;
1-[[*m*-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea.
$C_{24}H_{34}N_4O_5S$ 490.62

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
GLIMEPIRIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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