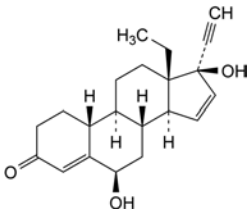
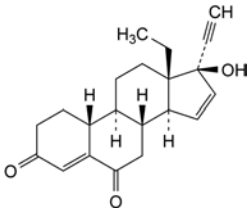
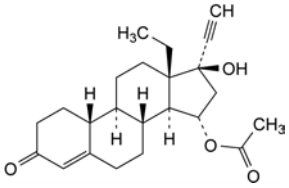


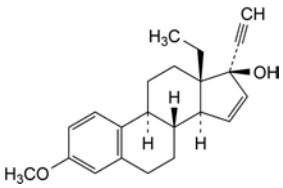
D. 13-ethyl-6β,17-dihydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one (6β-hydroxy-gestodene),



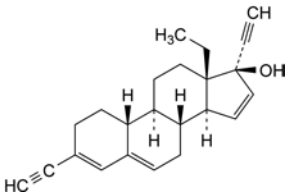
E. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yne-3,6-dione (6-keto-gestodene),



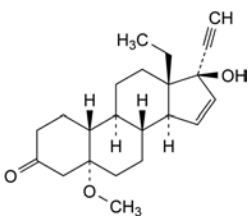
F. 13-ethyl-17-hydroxy-3-oxo-18,19-dinor-17α-pregn-4-en-20-yn-15α-yl acetate (15α-acetoxy-gestodene),



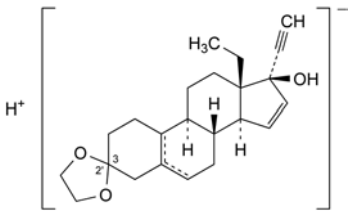
G. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-1,3,5(10),15-tetraen-20-yn-17-o1 (*A*-aromatic-gestodene),



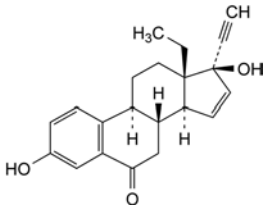
H. 13-ethyl-3-ethynyl-18,19-dinor-17α-pregna-3,5,15-trien-20-yn-17-o1 (diethynyl-gestodene),



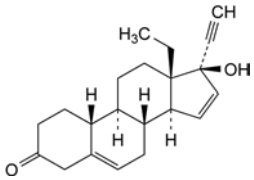
I. 13-ethyl-17-hydroxy-5-methoxy-18,19-dinor-5α,17α-pregn-15-en-20-yn-3-one (5-methoxy-gestodene),



J. 13-ethylspiro(18,19-dinor-17α-pregna-5,15-dien-20-yne-3,2′-[1,3]dioxolan)-17-ol and 13-ethylspiro(18,19-dinor-17α-pregna-5(10),15-dien-20-yne-3,2′-[1,3]dioxolan)-17-ol (gestodene ketal),



K. 13-ethyl-3,17-dihydroxy-18,19-dinor-17α-pregna-1,3,5(10),15-tetraen-20-yn-6-one (aromatic 6-keto-gestodene),

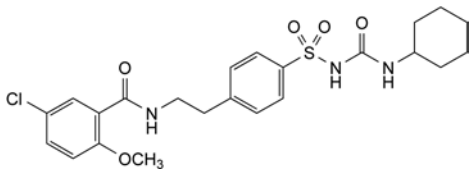


L. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5,15-dien-20-yn-3-one (Δ5(6)-gestodene).

01/2008:0718
corrected 7.0

GLIBENCLAMIDE

Glibenclamidum



$C_{23}H_{28}ClN_3O_5S$ M_r 494.0
[10238-21-8]

DEFINITION

1-[[4-[2-[(5-Chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]-3-cyclohexylurea.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol and in methanol.

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (*2.2.14*): 169 °C to 174 °C.

B. Dissolve 50.0 mg in *methanol R*, with the aid of ultrasound if necessary, and dilute to 50.0 mL with the same solvent. To 10.0 mL of the solution add 1.0 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *methanol R*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 300 nm and a less intense maximum at 275 nm. The specific absorbances at the maxima are 61 to 65 and 27 to 32, respectively.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of *potassium bromide R*.

Comparison: *glibenclamide CRS*.

If the spectra obtained show differences, moisten separately the substance to be examined and the reference substance with *methanol R*, triturate, dry at 100-105 °C and record the spectra again.

D. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Reference solution. Dissolve 10 mg of *glibenclamide CRS* in a mixture of equal volumes of *methanol R* and *methylene chloride R* and dilute to 10 mL with the same mixture of solvents.

Plate: *TLC silica gel GF_{254} plate R*.

Mobile phase: *alcohol R, glacial acetic acid R, cyclohexane R, methylene chloride R* (5:5:45:45 *V/V/V/V*).

Application: 10 µL.

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

E. Dissolve 20 mg in 2 mL of *sulfuric acid R*. The solution is colourless and shows blue fluorescence in ultraviolet light at 365 nm. Dissolve 0.1 g of *chloral hydrate R* in the solution. Within about 5 min, the colour changes to deep yellow and, after about 20 min, develops a brownish tinge.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent. Prepare immediately before use.

Reference solution (a). Dissolve 5.0 mg of *glibenclamide impurity A CRS* and 5.0 mg of *glibenclamide impurity B CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 20.0 mL with *methanol R*.

Reference solution (b). Dilute 2.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 50.0 mL with *methanol R*.

Reference solution (c). Dissolve 5 mg of *gliclazide CRS* in *methanol R*, add 2 mL of the test solution and dilute to 100 mL with *methanol R*. Dilute 1 mL of this solution to 10 mL with *methanol R*.

Column:

– *size*: *l* = 0.10 m, Ø = 4.6 mm,
– *stationary phase*: spherical *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (3 µm),
– *temperature*: 35 °C.

Mobile phase:

– *mobile phase A*: mix 20 mL of a 101.8 g/L solution of freshly distilled *triethylamine R* adjusted to pH 3.0 using *phosphoric acid R*, and 50 mL of *acetonitrile R*; dilute to 1000 mL with *water R*,
– *mobile phase B*: mobile phase A, *water R*, *acetonitrile R* (20:65:915 *V/V/V*),

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	45	55
15 - 30	45 → 5	55 → 95
30 - 40	5	95

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL.

Relative retention with reference to glibenclamide (retention time = about 5 min): impurity A = about 0.5; impurity B = about 0.6.

System suitability: reference solution (c):

– *resolution*: minimum 5.0 between the peaks due to glibenclamide and gliclazide.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), and not more than 2 such peaks have an area greater than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
– *total of other impurities*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),
– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with limit test D. Prepare the standard using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

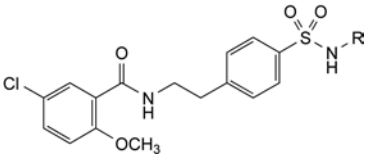
Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.400 g with heating in 100 mL of *alcohol R*. Titrate with *0.1 M sodium hydroxide*, using 1.0 mL of *phenolphthalein solution R* as indicator, until a pink colour is obtained.

1 mL of *0.1 M sodium hydroxide* is equivalent to 49.40 mg of $C_{23}H_{28}ClN_3O_5S$.

IMPURITIES



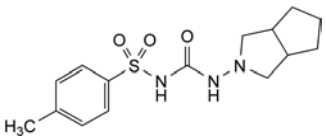
A. R = H: 5-chloro-2-methoxy-*N*-[2-(4-sulfamoylphenyl)ethyl]benzamide,

B. R = CO-OCH_3: methyl [[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl]sulfonyl]carbamate.

01/2008:1524
corrected 6.0

GLICLAZIDE

Gliclazidum



$C_{15}H_{21}N_3O_3S$ M_r 323.4
[21187-98-4]

DEFINITION

1-(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl)sulfonyl]urea.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *gliclazide CRS*.

TESTS

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

Solvent mixture: *acetonitrile R, water R* (45:55 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in 23 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 10.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 15 mg of *gliclazide impurity F CRS* in 23 mL of *acetonitrile R* and dilute to 50 mL with *water R*. Dilute 1 mL of this solution to 20 mL with the solvent mixture.

Reference solution (c). Dissolve 10.0 mg of *gliclazide impurity F CRS* 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 solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *triethylamine R, trifluoroacetic acid R, acetonitrile R, water R* (0.1:0.1:45:55 *V/V/V/V*).

Flow rate: 0.9 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 20 µL.

Run time: twice the retention time of gliclazide.

Relative retention with reference to gliclazide (retention time = about 16 min): impurity F = about 0.9.

System suitability: reference solution (b):

– *resolution*: minimum 1.8 between the peaks due to impurity F and gliclazide.

Limits:

– *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 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);
– *sum of impurities other than F*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Impurity B. Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Test solution. Dissolve 0.400 g of the substance to be examined in 2.5 mL of *dimethyl sulfoxide R* and dilute to 10.0 mL with *water R*. Stir for 10 min, store at 4 °C for 30 min and filter.

Reference solution. Dissolve 20.0 mg of *gliclazide impurity B CRS* 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*.

Injection: 50 µL.

Retention time: impurity B = about 8 min.

Limit:

– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (2 ppm).

Heavy metals (*2.4.8*): maximum 10 ppm.

1.5 g complies with test F. Prepare the reference solution using 1.5 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.25 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

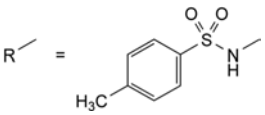
Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 32.34 mg of $C_{15}H_{21}N_3O_3S$.

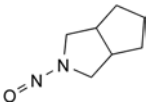
IMPURITIES

Specified impurities: B, F.

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*): *A, C, D, E, G.*



A. R-H: 4-methylbenzenesulfonamide,



B. 2-nitroso-octahydrocyclopenta[*c*]pyrrole,

C. R-CO-O-C_2H_5: ethyl [(4-methylphenyl)sulfonyl]carbamate,