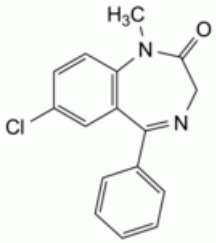
Edition: BP 2025 (Ph. Eur. 11.6 update)

Diazepam

General Notices

(Ph. Eur. monograph 0022)



$C_{16}H_{13}ClN_2O$ 284.7 *439-14-5*

Action and use

Benzodiazepine.

Preparations

Diazepam Injection

Diazepam Oral Solution

Diazepam Rectal Solution

Diazepam Tablets

Ph Eur

DEFINITION

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very slightly soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison: *diazepam CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from bright light.*

Test solution Dissolve 25.0 mg of the substance to be examined in 0.5 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

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

Reference solution (b) Dissolve the contents of a vial of *diazepam for system suitability CRS* (containing impurities A, B and E) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.15 m, *Ø* = 4.6 mm;

— *stationary phase*: spherical *end-capped octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 22 volumes of *acetonitrile R*, 34 volumes of *methanol R* and 44 volumes of a 3.4 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *dilute sodium hydroxide solution R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time About 4 times the retention time of diazepam.

Identification of impurities Use the chromatogram supplied with *diazepam for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and E.

Relative retention With reference to diazepam (retention time = about 9 min): impurity E = about 0.7; impurity A = about 0.8; impurity B = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities E and A and minimum 6.0 between the peaks due to impurity A and diazepam.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.3; impurity E = 1.3;

— *impurities A, B, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (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);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *acetic anhydride 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 28.47 mg of $C_{16}H_{13}ClN_2O$.

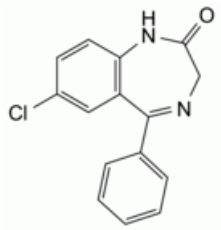
STORAGE

Protected from light.

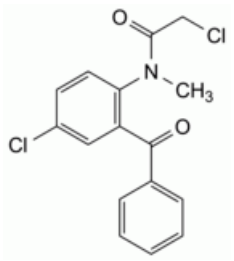
IMPURITIES

Specified impurities A, B, E.

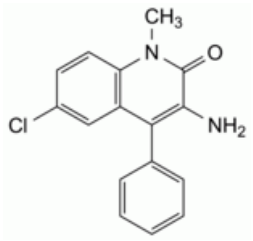
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



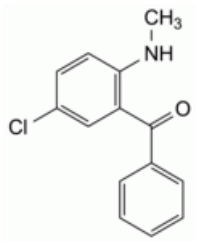
A. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (nordazepam),



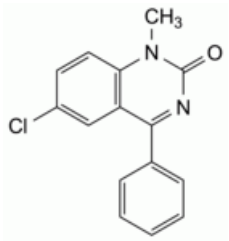
B. *N*-(2-benzoyl-4-chlorophenyl)-2-chloro-*N*-methylacetamide,



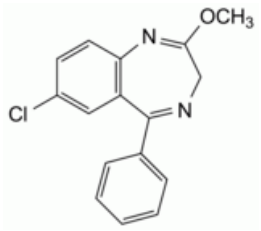
C. 3-amino-6-chloro-1-methyl-4-phenylquinolin-2(1*H*)-one,



D. [5-chloro-2-(methylamino)phenyl]phenylmethanone,



E. 6-chloro-1-methyl-4-phenylquinazolin-2(1*H*)-one,



F. 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine.

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