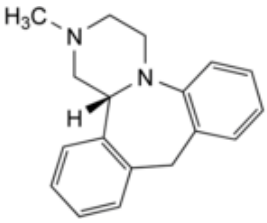
Edition: BP 2025 (Ph. Eur. 11.6 update)

Mianserin Hydrochloride

General Notices

(Ph. Eur. monograph 0846)



and enantiomer , HCl

$C_{18}H_{21}ClN_2$ 300.8 *21535-47-7*

Action and use

Monoamine reuptake inhibitor; tetracyclic antidepressant.

Preparation

Mianserin Tablets

Ph Eur

DEFINITION

(14b*RS*)-2-Methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c,f*]pyrazino[1,2-*a*]azepine hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder or crystals.

Solubility

Sparingly soluble in water and in methylene chloride, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50.0 mg in *water R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 50.0 mL with *water R*.

Spectral range 230-350 nm.

Absorption maximum At 279 nm.

Specific absorbance at the absorption maximum 64 to 72.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *mianserin hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution (a) Dissolve 10 mg of *mianserin hydrochloride CRS* in *methylene chloride R* and dilute to 5 mL with the same solvent.

Reference solution (b) Dissolve 10 mg of *mianserin hydrochloride CRS* and 10 mg of *cyproheptadine hydrochloride CRS* in *methylene chloride R* and dilute to 5 mL with the same solvent.

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

Mobile phase *diethylamine R*, *ether R*, *cyclohexane R* (5:20:75 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated principal spots.

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 reference solution (a).

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

pH (*2.2.3*)

4.0 to 5.5.

Dissolve 0.10 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Buffer solution pH 3.0 Dissolve 5.0 g of *sodium octanesulfonate R* in *water R* and dilute to 350 mL with the same solvent. Stir until complete dissolution. Adjust to pH 3.0 with a mixture of 1 volume of *phosphoric acid R* and 3 volumes of *water R*. Dilute to 400 mL with *water R*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25.0 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 *mianserin for system suitability CRS* (containing impurities A, D and E) in 1.0 mL of the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *mianserin impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

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

Mobile phase Buffer solution pH 3.0, *methanol R* (37:63 *V/V*).

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Run time Twice the retention time of mianserin.

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

Relative retention With reference to mianserin (retention time = about 18 min): impurity B = about 0.2; impurity A = about 0.5; impurity D = about 0.7; impurity E = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 4.0, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mianserin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 2.4; impurity D = 2.1;

— *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities A, D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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 65 °C at a pressure not exceeding 0.7 kPa for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 30.08 mg of $C_{18}H_{21}ClN_2$.

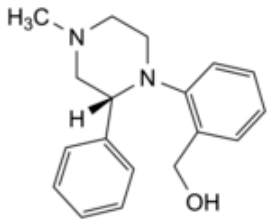
STORAGE

Protected from light.

IMPURITIES

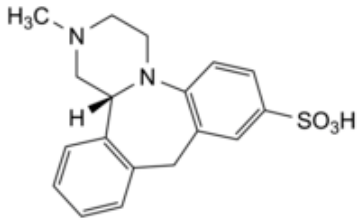
Specified impurities A, B, D, E.

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, F.



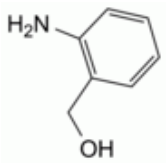
and enantiomer

A. [2-[(2*RS*)-4-methyl-2-phenylpiperazin-1-yl]phenyl]methanol,

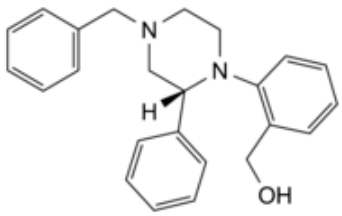


and enantiomer

B. (14b*RS*)-2-methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine-8-sulfonic acid,

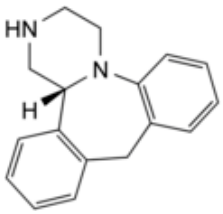


C. (2-aminophenyl)methanol,



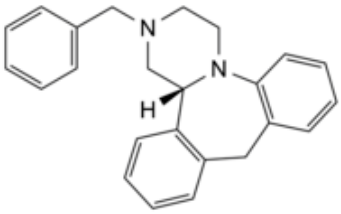
and enantiomer

D. [2-[(2*RS*)-4-benzyl-2-phenylpiperazin-1-yl]phenyl]methanol,



and enantiomer

E. (14b*RS*)-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine,



and enantiomer

F. (14b*RS*)-2-benzyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine.

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