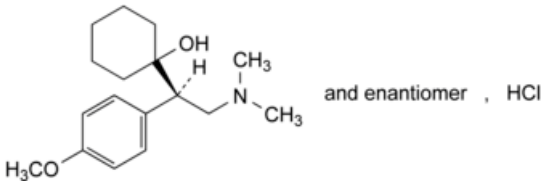
Edition: BP 2025 (Ph. Eur. 11.6 update)

Venlafaxine Hydrochloride

General Notices

(Ph. Eur. monograph 2119)



$C_{17}H_{28}ClNO_2$ 313.9 *99300-78-4*

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

Preparations

Venlafaxine Prolonged-release Capsules

Venlafaxine Prolonged-release Tablets

Venlafaxine Tablets

Ph Eur

DEFINITION

1-[(1*RS*)-2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *venlafaxine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *2-propanol R*, evaporate to dryness and record new spectra using the residues.

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

TESTS

Acidity or alkalinity

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent. Add 0.05 mL of *methyl red solution R* and 0.1 mL of *0.01 M hydrochloric acid*. The solution is pink. Not more than 0.2 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 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 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *venlafaxine for system suitability CRS* (containing impurities D and F) in 1.0 mL of the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm.

Mobile phase Mix 510 volumes of *acetonitrile R* and 1490 volumes of a solution prepared as follows: dissolve 17 g of *ammonium dihydrogen phosphate R* in 1490 mL of *water R* and adjust to pH 4.4 using *phosphoric acid R*.

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 20 µL.

Run time 10 times the retention time of venlafaxine.

Relative retention With reference to venlafaxine (retention time = about 9 min): impurity D = about 0.9; impurity F = about 3.4.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and venlafaxine.

Limits:

— *impurity F*: 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 80 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

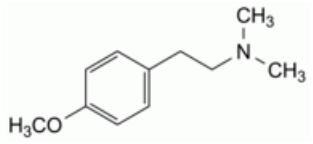
Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion. Carry out a blank titration.

1 mL of *0.1 M sodium hydroxide* is equivalent to 31.39 mg of $C_{17}H_{28}ClNO_2$.

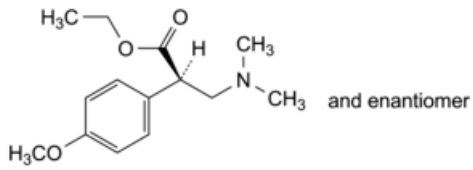
IMPURITIES

Specified impurities *F.*

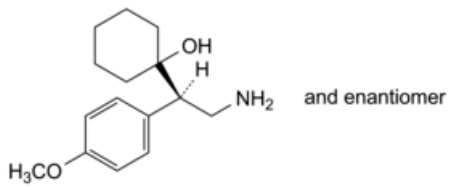
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



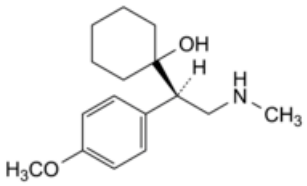
A. 2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



B. ethyl (2*RS*)-3-(dimethylamino)-2-(4-methoxyphenyl)propanoate,

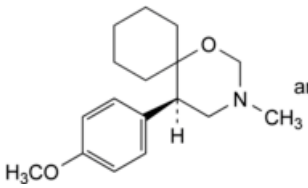


C. 1-[(1*RS*)-2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol,



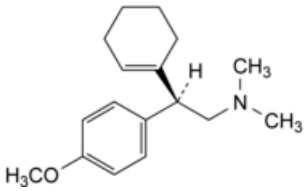
and enantiomer

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol,



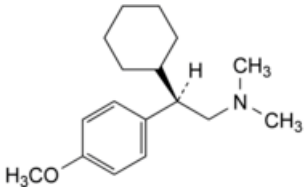
and enantiomer

E. (5*RS*)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane,



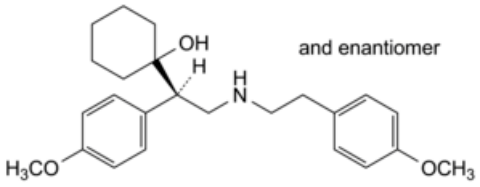
and enantiomer

F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N,N*-dimethylethanamine,



and enantiomer

G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N,N*-dimethylethanamine,



and enantiomer

H. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]cyclohexanol.

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