Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.6; impurity C = 1.4;
- *impurities A, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);
- *unspecified impurities*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
- *total*: not more than 2.8 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);
- *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Water (*2.5.12*): maximum 4.0 per cent, determined on 0.300 g.

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

ASSAY

Dissolve 0.450 g in 50 ml of *glacial 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 63.8 mg of $C_{34}H_{57}BrN_2O_4$.

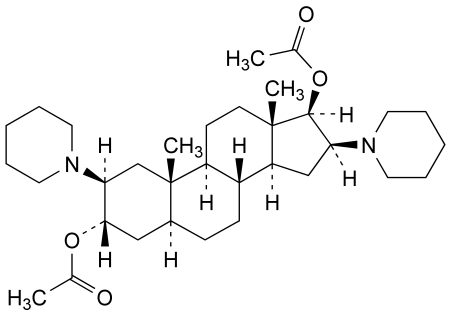
STORAGE

In an airtight container, protected from light and moisture.

IMPURITIES

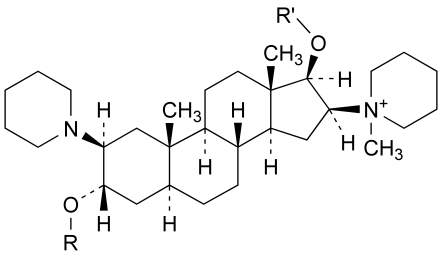
Specified impurities: A, B, C, D, E.

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*): *F.*



A. 2β,16β-bis(piperidin-1-yl)-5α-androstane-3α,17β-diyl diacetate,

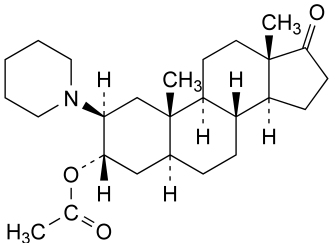
B. pancuronium,



C. R = H, R′ = CO-CH_3: 1-[17β-(acetyloxy)-3α-hydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidinium,

D. R = R′ = H: 1-[3α,17β-dihydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidinium,

E. R = CO-CH_3, R′ = H: 1-[3α-(acetyloxy)-17β-hydroxy-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidinium,

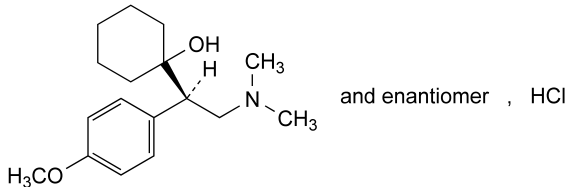


F. 2β-(piperidin-1-yl)-17-oxo-5α-androstan-3α-yl acetate.

01/2008:2119

VENLAFAXINE HYDROCHLORIDE

Venlafaxini hydrochloridum



$C_{17}H_{28}ClNO_2$ M_r 313.9
[99300-78-4]

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).

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

Dissolve 1.0 g in 20 ml of *water R*. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

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.

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

ASSAY

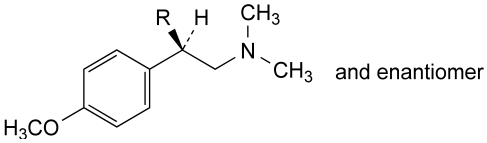
Dissolve 0.250 g in a mixture of 5.0 ml of *0.01 M hydrochloric acid* and 50 ml of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion. Carry out a blank titration.

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.

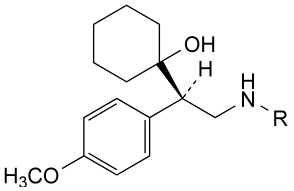
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



and enantiomer

A. R = H: 2-(4-methoxyphenyl)-*N,N*-dimethylethanamine,

B. R = CO-O-C_2H_5: ethyl (2*RS*)-3-(dimethylamino)-2-(4-methoxyphenyl)propanoate,

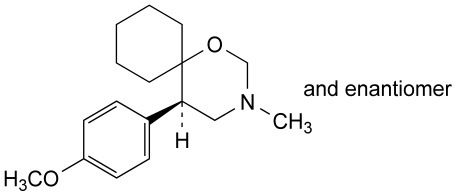


and enantiomer

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

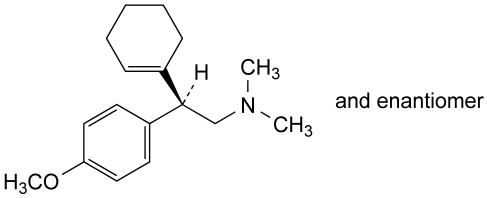
D. R = CH_3: 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol,

H. R = CH_2-CH_2-C_6H_4-*p*-OCH_3: 1-[(1*RS*)-1-(4-methoxyphenyl)-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]cyclohexanol,



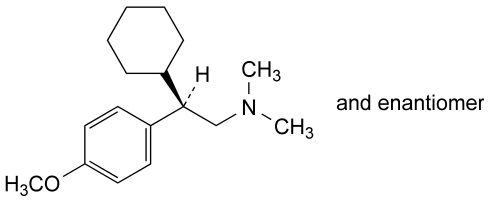
and enantiomer

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,

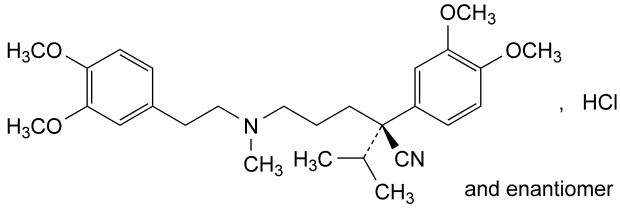


G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine.

01/2008:0573
corrected 6.0

VERAPAMIL HYDROCHLORIDE

Verapamili hydrochloridum



$C_{27}H_{39}ClN_2O_4$ M_r 491.1
[152-11-4]

DEFINITION

(2*RS*)-2-(3,4-Dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)-ethyl](methyl)amino]-2-(1-methylethyl)pentanenitrile hydrochloride.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent).

mp: about 144 °C.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 20.0 mg in *0.01 M hydrochloric acid* and dilute to 100.0 ml with the same acid. Dilute 5.0 ml of this solution to 50.0 ml with *0.01 M hydrochloric acid.*

Spectral range: 210-340 nm.

Absorption maxima: at 229 nm and 278 nm.

Shoulder: at 282 nm.

Absorbance ratio: A_{278}/A_{229} = 0.35 to 0.39.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *verapamil hydrochloride CRS.*

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 20 mg of *verapamil hydrochloride CRS* in *methylene chloride R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 5 mg of *papaverine hydrochloride CRS* in reference solution (a) and dilute to 5 ml with reference solution (a).

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

Mobile phase: *diethylamine R, cyclohexane R* (15:85 *V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in air.

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 (b) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* while gently heating and dilute to 20.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.0 for solution S.

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the initial mobile phase composition and dilute to 10.0 ml with the initial mobile phase composition.

Reference solution (a). Dissolve 5 mg of *verapamil hydrochloride CRS*, 5 mg of *verapamil impurity I CRS* and 5 mg of *verapamil impurity M CRS* in the initial mobile phase composition and dilute to 20 ml with the initial mobile phase composition. Dilute 1 ml of this solution to 10 ml with the initial mobile phase composition.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the initial mobile phase composition. Dilute 1.0 ml of this solution to 10.0 ml with the initial mobile phase composition.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase:

– *mobile phase A*: 6.97 g/l solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.20 with *phosphoric acid R*;

– *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 22	63	37
22 - 27	63 → 35	37 → 65
27 - 35	35	65
35 - 36	35 → 63	65 → 37
36 - 50	63	37

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 278 nm.

Monographs T-Z