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

Venlafaxine Prolonged-release Capsules

General Notices

Prolonged-release Venlafaxine Capsules

Venlafaxine Prolonged-release Capsules from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Inhibition of 5HT and noradrenaline reuptake; antidepressant.

DEFINITION

Venlafaxine Prolonged-release Capsules contain Venlafaxine Hydrochloride. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Venlafaxine Hydrochloride. The dissolution profile reflects the performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of venlafaxine, $C_{17}H_{27}NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered capsule contents containing the equivalent of 0.35 g of venlafaxine with 100 mL of a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane* for 30 minutes, filter the extract through *anhydrous sodium sulfate* and evaporate the filtrate to dryness. Wash the residue with a mixture of 30 volumes of *cyclohexane* and 70 volumes of *dichloromethane*, filter and dry the residue. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of venlafaxine hydrochloride *(RS 439)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase A.

(1) Mix with the aid of ultrasound, a quantity of the powdered capsule contents containing the equivalent of 200 mg of venlafaxine with 80 mL of a 2.4% v/v solution of *orthophosphoric acid*, shake for a further 30 minutes, cool, add sufficient *water* to produce 100 mL, mix and centrifuge; use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 500 volumes.

(3) 0.2% w/v of *venlafaxine impurity standard BPCRS*.
(4) Dilute 25 volumes of solution (2) to 100 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Partisil ODS 3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 226 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *triethylamine*, 20 volumes of *acetonitrile* and 80 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

Mobile phase B 1 volume of *triethylamine*, 50 volumes of *acetonitrile* and 50 volumes of *water* adjusted to pH 3.5 with *orthophosphoric acid*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-30	100→0	0→100	linear gradient
30-45	0	100	isocratic
45-48	0→100	100→0	re-equilibration
48-60	100	0	isocratic

Under the prescribed conditions, the retention time of venlafaxine is about 13 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D or impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (4) (0.05%).

ASSAY

Mix the contents of 20 capsules. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the capsule contents containing the equivalent of 175 mg of venlafaxine for 30 minutes with 50 mL of *methanol*, add sufficient *methanol* to produce 100 mL, mix and filter. To 5 volumes of the filtrate add sufficient of the mobile phase to produce 100 volumes.
(2) 0.01% w/v of *venlafaxine hydrochloride BPCRS*.
(3) 0.01% w/v of *venlafaxine impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C18 is suitable)
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 226 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

20 volumes of *acetonitrile* and 80 volumes of a 1% v/v solution of *triethylamine* previously adjusted to pH 3.0 with *orthophosphoric acid*.

Under the prescribed conditions, the retention time of venlafaxine is about 3.5 minutes. If necessary adjust the *acetonitrile* content of the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity D and venlafaxine is at least 1.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{27}NO_2$ in the capsules using the declared content of $C_{17}H_{27}NO_2$,HCl in *venlafaxine hydrochloride BPCRS*. Each mg of $C_{17}H_{27}NO_2$,HCl is equivalent to 0.884 mg of $C_{17}H_{27}NO_2$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of venlafaxine.

IMPURITIES

The impurities limited by the requirements of this monograph include:

D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol (European Pharmacopoeia impurity D);
F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-N,N-dimethylethanamine (European Pharmacopoeia impurity F).