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

Vardenafil Tablets

General Notices

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase type V with vasodilator action; treatment of erectile dysfunction.

DEFINITION

Vardenafil Tablets contain Vardenafil Hydrochloride Trihydrate.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of vardenafil, $C_{23}H_{32}N_6O_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of the powdered tablets containing the equivalent of 20 mg of vardenafil in 100 mL of a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid* and filter.
(2) 0.02% w/v of *vardenafil hydrochloride EPCRS* in a solution of 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use precoated *silica gel F_{254} plates* (Merck silica gel 60 F_{254} HPTLC plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 8 cm.
(e) After removal of the plate, dry in air, and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume each of *acetone*, of *cyclohexane* and of *methanol*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for liquid chromatography, Appendix III D, using the following solutions protected from light.

(1) After 30 minutes withdraw a sample of the medium. Use the filtered dissolution medium diluted, if necessary, to obtain a solution expected to contain the equivalent of 0.00025% w/v of vardenafil.
(2) 0.00027% w/v of *vardenafil hydrochloride EPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 3 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.8 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 245 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

27 volumes of *acetonitrile* and 73 volumes of 0.68% w/v *potassium dihydrogenphosphate* adjusted to pH 3.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, HCl, in *vardenafil hydrochloride EPCRS*. Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

LIMITS

The amount of vardenafil released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions

Solvent A 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in 50 mL of solvent A with the aid of ultrasound and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solvent A.
(3) Dilute 1 volume of solution (2) to 10 volumes with solvent A.
(4) 0.015% w/v of *vardenafil for system suitability EPCRS* solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Extend C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 245 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08% w/v of *ammonium acetate* in 90 volumes of water and 10 volumes of *acetonitrile*.

Mobile phase B 0.08% w/v *ammonium acetate* in 10 volumes of water and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	80→0	20→100	linear gradient
20-21	0→80	100→20	linear gradient
21-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to vardenafil (retention time about 8 min) are: impurity B, about 0.2; impurity 1, about 0.5; impurity 2, about 0.55; impurity A, about 0.6 and impurity C, about 1.3.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to vardenafil and impurity A is not less than 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak due to impurity A or impurity 1 is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the area of any peak due to impurity 2 is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all *secondary peaks*, excluding impurities A, 1 and 2, is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of vardenafil comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solvent A 1 volume of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.
(1) Shake one tablet with sufficient volume of solvent A to produce a solution expected to contain 0.02% w/v of vardenafil and filter.
(2) 0.0215% w/v of *vardenafil hydrochloride EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax Extend C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 245 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.08% w/v of *ammonium acetate* in 90 volumes of water and 10 volumes of *acetonitrile*.

Mobile phase B 0.08% w/v *ammonium acetate* in 10 volumes of water and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	70→10	30→90	linear gradient
10-11	10→70	90→30	linear gradient
11-15	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention time of the vardenafil peak is about 5 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the *resolution* between the peak due to vardenafil and impurity A is not less than 4.0.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, in *vardenafil hydrochloride EPCRS*. Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of vardenafil

Use the average individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of vardenafil

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

Solvent A 1 volumes of *acetonitrile* and 4 volumes of 0.1M *hydrochloric acid*.

(1) Disperse a quantity of powdered tablets containing the equivalent of 10 mg of vardenafil in solvent A with the aid of ultrasound, dilute to 50 mL and filter.
(2) 0.0215% w/v of *vardenafil hydrochloride EPCRS* in solvent A.
(3) 0.015% w/v of *vardenafil for system suitability EPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to vardenafil and impurity A is not less than 5.0.

DETERMINATION OF CONTENT

Calculate the content of vardenafil, $C_{23}H_{32}N_6O_4S$, using the declared content of $C_{23}H_{32}N_6O_4S$, HCl, in *vardenafil hydrochloride EPCRS*. Each mg of *vardenafil hydrochloride EPCRS* is equivalent to 0.9306 mg of vardenafil.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Vardenafil Hydrochloride Trihydrate and:

1. 1-Ethyl-4-{4-ethoxy-3-[5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-*f*][1,2,4]triazin-2-yl]benzenesulfonyl}piperazine *N*^{1}-oxide

2. 2-[2-Ethoxy-5-(piperazine-1-sulfonyl)phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one