

BRIEFING

Venlafaxine Extended-Release Capsules. A new USP Pending Monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the *Assay* and in the tests for *Dissolution* and *Organic Impurities* are based on analyses performed with a Zorbax SB-C18 brand of L1 column. In the test for *Organic Impurities*, the typical retention time for venlafaxine related compound A is 6.1 min. In the *Assay* and the test for *Organic Impurities*, the typical retention time for the venlafaxine peak is 6.8 min. In the *Dissolution* test, the typical retention time for the venlafaxine peak is 2.6 min.

(MD-PP: H. Ramanathan, R. Ravichandran. BPC: M. Marques.) RTS—46683

Add the following:

►Venlafaxine Extended-Release Capsules

Draft 1

DEFINITION

Venlafaxine Extended Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of venlafaxine free base (C₁₇H₂₇NO₂).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** (197U)
Wavelength range: 250–310 nm
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Mobile phase: Acetonitrile, triethylamine, and water (25:0.4:75). Adjust with phosphoric acid to a pH of 3.5.
Standard solution: 0.25 mg/mL of USP Venlafaxine Hydrochloride RS in *Mobile phase*
Sample stock solution: Equivalent to 100 mg of venlafaxine (from contents of NLT 10 capsules) in a 100-mL volumetric flask. Add 8 mL of acetonitrile, and shake for 40 min. Add 50 mL of *Mobile phase*, and shake for an additional 20 min. Dilute with *Mobile phase* to volume. Pass a portion through a suitable filter having a porosity of 0.45 μm.
Sample solution: 0.25 mg/mL of venlafaxine (from filtrate in *Sample stock solution*) in *Mobile phase*.
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: UV 226 nm
Column: 4.6-mm × 25-cm column; 5-μm packing L1
Flow rate: 1 mL/min
Injection size: 10 μL
Run time: 1.5 times the retention time of venlafaxine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of C₁₇H₂₇NO₂ in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

- r_U = peak response of the *Sample solution*
- r_S = peak response of the *Standard solution*
- C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

- C_U = nominal concentration of venlafaxine in the *Sample solution* (mg/mL)
- M_{r1} = molecular weight of venlafaxine, 277.40
- M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** (711)
Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 3, 6, 16, and 24 h
Mobile phase: Acetonitrile, triethylamine, and water (45:0.4:55). Adjust with phosphoric acid to a pH of 3.5.
Standard solution: 0.05 mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter having a porosity of 0.45 μm.
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: UV 274 nm
Column: 4.6-mm × 25-cm; 5-μm packing L1
Flow rate: 1 mL/min
Injection size: 30 μL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.5
Relative standard deviation: NMT 2.0%
Calculate the concentration, C_t, of venlafaxine in *Medium* (mg/mL) after t hours:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

- r_U = peak response of the *Sample solution*
- r_S = peak response of the *Standard solution*
- C_S = concentration of the *Standard solution* (mg/mL)
- M_{r1} = molecular weight of venlafaxine, 277.40
- M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of venlafaxine dissolved at the first time interval:

$$\text{Result} = (C_1/L) \times V \times 100$$

- C₁ = concentration of venlafaxine in *Medium* after 3 h (mg/mL)
 - V = volume of *Medium*, 900 mL
 - L = label claim (mg)
- Calculate the percentage of venlafaxine dissolved at the second time interval:

$$\text{Result} = (C_2/L) \times (900 - V) + (C_1 \times V) \times 100$$

- C₂ = concentration of venlafaxine in *Medium* after 6 h (mg/mL)
 - V = aliquot sampled (mL)
- Calculate the percentage of venlafaxine dissolved at the nth time interval:

$$\text{Result} = (C_n/L) \times (900 - [(n-1) \times V]) + [(C_1 + C_2 + C_{n-1}) \times V] \times 100$$

- C_n = concentration of venlafaxine in *Medium* after n hours (mg/mL)

Tolerances: The percentages of the labeled amount of venlafaxine dissolved at the times specified conform to *Acceptance Table 2*.

Time (h)	Amount Dissolved
3	NMT 40%
6	35%–60%
16	60%–85%
24	NLT 75%

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES**Organic Impurities**• **PROCEDURE**

Mobile phase: Proceed as directed for Assay.

Standard solution: Proceed as directed for Assay.

System suitability solution: 0.25 µg/mL of USP Venlafaxine Related Compound A RS in *Standard solution*

Sample solution: Proceed as directed for Assay.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 10 µL

Run time: 4 times the retention time of venlafaxine

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention time for venlafaxine related compound A is 0.9.]

Suitability requirements

Resolution: NLT 1.5 between the peaks for venlafaxine related compound A and venlafaxine

Tailing factor: NMT 2.0 for the venlafaxine peak

Relative standard deviation: NMT 5.0% for the venlafaxine peak

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

- r_U = peak response for an individual impurity from the *Sample solution*
- r_S = peak response for venlafaxine from the *Standard solution*
- C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of venlafaxine in the *Sample solution* (mg/mL)
- M_{r1} = molecular weight of venlafaxine, 277.40
- M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Acceptance criteria

Individual impurities: NMT 0.20%

Total impurities: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.

• **USP REFERENCE STANDARDS (11)**

USP Venlafaxine Hydrochloride RS

USP Venlafaxine Related Compound A RS₁ (1-Mar-2010)