

BRIEFING

Venlafaxine Extended-Release Capsules. This monograph was posted on the USP Pending Monographs web page for public comment on August 28, 2009. The Monograph Development—Psychiatrics and Psychoactives and Biopharmaceutics Expert Committees have reviewed the comments that were received and have approved the monograph as an Authorized USP Pending Monograph. The following is a summary of the comments received.

- (1) *Comment 1:* Commenter requested that the limits proposed for individual impurities in the test for *Organic Impurities* be revised to match ICH guidelines for identification threshold which is also consistent with commenters ANDA.
Response 1: Comment incorporated.
- (2) *Comment 2:* For the *Dissolution* test, commenter requested to change the filter specification from 0.45 μm to 20 μm.
Response 2: Comment incorporated with the inclusion of the phrase “suitable filter” which allows users the flexibility to use the appropriate filter.
- (3) *Comment 3:* Commenter informed the title of the product monograph does not account for the established nonproprietary name submitted to the FDA at the time of product approval.
Response 3: Comment not incorporated because the comment is from a manufacturer of the dosage form that has been fully approved by the FDA in the United States. In addition, the commenters proposed title for this drug product is inconsistent with USP’s current nomenclature policy.
- (4) *Comment 4:* Commenter informed that the *Dissolution* test included in the proposal is not consistent with the dissolution profile inherent to this product and currently approved by the FDA. Commenter requested USP to include the time points, tolerances, and methodology consistent with the FDA-approved criteria.
Response 4: Comment not incorporated as the tests and acceptance criteria in the draft Pending Monograph are from a sponsor whose application is under review by the FDA. Because the comment is from a manufacturer of the dosage form that has been fully approved by the FDA in the United States, the comments and supporting data will be reviewed for publication in a future edition of *PF*. If the sponsor of the Pending Monograph receives full approval from the FDA during the *PF* publication process, the monograph submissions from the commenter and this Authorized Pending Monograph will be reconciled per the USP policies for adoption using the flexible monograph approach.

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.

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Venlafaxine Extended-Release Capsules

v.1 Authorized April 1, 2010

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 the 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 of 0.45-μm pore size.
Sample solution: 0.25 mg/mL of venlafaxine (from filtrate in the *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; 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% venlafaxine free base

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 through a suitable filter.
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

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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:

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

C_1 = concentration of venlafaxine in *Medium* after 3 h (mg/mL)

L = Capsule label claim (mg)

V = volume of *Medium*, 900 mL

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

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

C_2 = concentration of venlafaxine in *Medium* after 6 h (mg/mL)

L = Capsule label claim (mg)

V = aliquot sampled (mL)

C_1 = concentration of venlafaxine in *Medium* after 3 h (mg/mL)

Calculate the percentage of venlafaxine dissolved at the n th 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)

L = Capsule label claim (mg)

V = volume of *Medium*, 900 mL

C_1 = concentration of venlafaxine in *Medium* after 3 h (mg/mL)

C_2 = concentration of venlafaxine in *Medium* after 6 h (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%

Time (h)	Amount Dissolved
16	60%–85%
24	NLT 75%

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

IMPURITIES

Organic Impurities

• PROCEDURE

Mobile phase, Standard solution, and Sample solution:

Proceed as directed in the *Assay*.

System suitability solution: 0.25 μg/mL of USP Venlafaxine

Related Compound A RS in *Standard solution*

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: *Standard solution* and *Sample 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 each 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 0.2%

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 RS