# CLINICAL UPDATE

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| **Brand Name** | venlafaxine besylate |
| **Generic Name** | venlafaxine besylate |
| **Drug Manufacturer** | Norwich Pharmaceuticals, Inc. |

## Clinical Update

### TYPE OF CLINICAL UPDATE

New Active Ingredient and Dosage Form

### FDA APPROVAL DATE

June 29, 2022

### LAUNCH DATE

July 19, 2022

### REVIEW DESIGNATION

Standard

### TYPE OF REVIEW

Type 2 - New Active Ingredient and Type 3 - New Dosage Form; New Drug Application (NDA): 215429

### DISPENSING RESTRICTIONS

N/A

## Overview

### INDICATION(S) FOR USE

Venlafaxine Extended-Release Tablets are a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated in adults for the treatment of:

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)

### MECHANISMS OF ACTION

The mechanism of action of venlafaxine in treatment of MDD and GAD is unclear but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of reuptake of serotonin and norepinephrine.

### DOSAGE FORM(S) AND STRENGTH(S)

Extended-Release tablets: 112.5 mg

### DOSE & ADMINISTRATION

- Initiated at 112.5 mg once daily in patients who have received at least 75 mg of another venlafaxine extended-release product for at least 4 days.
- Maximum recommended dosage is 225 mg once daily.

- When discontinuing treatment, reduce the dose gradually. Gradual dosage reduction will require the use of another venlafaxine extended-release product.

## EFFICACY

**Generalized Anxiety Disorder:** The efficacy of Venlafaxine Extended-Release Tablets for the treatment of Generalized Anxiety Disorder (GAD) in adult patients is based upon adequate and well-controlled studies of venlafaxine extended-release capsules. The results of these adequate and well-controlled studies of venlafaxine extended-release capsules are presented below.

The efficacy of venlafaxine extended-release capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies of 75 mg to 225 mg per day, one 6- month, placebo-controlled, flexible-dose study of 75 mg to 225 mg per day), and one 6-month, placebo controlled, fixed-dose study of 37.5 mg, 75 mg, and 150 mg per day in adult outpatients meeting DSM-IV criteria for GAD [Venlafaxine Extended-Release Tablets are only available in 112.5 mg dosage strength].

In one 8-week study, venlafaxine extended-release capsules demonstrated superiority over placebo for the 75 mg, 150 mg, and 225 mg per day doses as measured by the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the Clinical Global Impressions (CGI) scale. However, the 75 mg and 150 mg per day doses were not as consistently effective as the highest dose (Study 1). A second 8-week study evaluating doses of 75 mg and 150 mg per day and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg per day dose was more consistently effective than the 150 mg per day dose (Study 2). A dose-response relationship for effectiveness in GAD was not clearly established in the 75 mg to 225 mg per day dose range studied.

Two 6-month studies, one evaluating venlafaxine extended-release capsules doses of 37.5 mg, 75 mg, and 150 mg per day (study 3) and the other evaluating venlafaxine extended-release capsules doses of 75 mg to 225 mg per day (study 4), showed that daily doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale during 6 months of treatment. While there was also evidence for superiority over placebo for the 37.5 mg per day dose, this dose was not as consistently effective as the higher doses.

Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

**Table 1: Primary Efficacy Results for Studies in Generalized Anxiety Disorder in Adults (Studies 1, 2, 3, and 4)**

| Study Number | Treatment Group | Primary Efficacy Measure: HAM-A Score | | |
|---|---|---|---|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE)* | Placebo Subtracted Difference[b] (95% CI) |
| Study 1 | Venlafaxine extended-release capsules 75 mg[a] | 24.7 | -11.1 (0.95) | -1.5 (-3.8, 0.8) |
| | 150 mg[a] | 24.5 | -11.7 (0.87) | -2.2 (-4.5, 0.1) |
| | 225 mg | 23.6 | -12.1 (0.81) | -2.6 (-4.9, -0.3) |
| | Placebo | 24.1 | -9.5 (0.85) | |

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| Study 2 | Venlafaxine extended-release capsules 75 mg[a] | 23.7 | -10.6 (0.82) | -2.6 (-4.6, -0.5) |
| | 150 mg[a] | 23.0 | -9.8 (0.86) | -1.7 (-3.8, 0.3) |
| | Placebo | 23.7 | -8.0 (0.73) | |
| Study 3 | Venlafaxine extended-release capsules 37.5 mg[a] | 26.6 (0.4) | -13.8 | -2.8 (-5.1, -0.6) |
| | 75 mg[a] | 26.3 (0.4) | -15.5 | -4.6 (-6.9, -2.3) |
| | 150 mg[a] | 26.3 (0.4) | -16.4 | -5.5 (-7.8, -3.1) |
| | Placebo | 26.7 (0.5) | -11.0 | |
| Study 4 | Venlafaxine extended-release capsules 75 mg[a] to 225 mg | 25.0 | -13.4 (0.79) | - 4.7 (-6.6, -2.9) |
| | Placebo | 24.9 | -8.7 (0.70) | |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a] Venlafaxine Extended-Release Tablets are only available as 112.5 mg dosage strength.

[b] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

**Major Depressive Disorder:** The efficacy of Venlafaxine Extended-Release Tablets for the treatment of major depressive disorder (MDD) in adult patients is based upon adequate and well-controlled studies of venlafaxine extended-release capsules. The results of these adequate and well-controlled studies of venlafaxine extended-release capsules are presented below

The efficacy of venlafaxine extended-release capsules as a treatment for Major Depressive Disorder (MDD) was established in two placebo-controlled, short-term (8 weeks for study 1; 12 weeks for study 2), flexibledose studies, with doses starting at 75 mg per day and ranging to 225 mg per day in adult outpatients meeting DSM-III-R or DSM-IV criteria for MDD [Venlafaxine Extended-Release Tablets are only available in 112.5 mg dosage strength]. In moderately depressed outpatients, the initial dose of venlafaxine was 75 mg per day. In both studies, venlafaxine extended-release capsules demonstrated superiority over placebo on the primary efficacy measure defined as change from baseline in the HAM-D-21 total score to the endpoint visit. Venlafaxine extended-release capsules also demonstrated superiority over placebo on the key secondary efficacy endpoint, the Clinical Global Impressions (CGI) Severity of Illness scale. Examination of gender subsets of the population studied did not reveal any differential responsiveness on the basis of gender.

In a longer-term study, adult outpatients with MDD who had responded during an 8-week open-label study on venlafaxine extended-release capsules 75 mg, 150 mg, or 225 mg, once daily every morning were randomized to continuation of their same venlafaxine extended-release capsules dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a CGI Severity of Illness item score of ≤3 and a HAM-D-21 total score of ≤10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity of Illness item score of ≥4 (moderately ill), (2) 2 consecutive CGI Severity of Illness item scores of ≥4, or (3) a final CGI Severity of Illness item score of ≥4 for any patient who withdrew from the study for any reason. Patients receiving continued

venlafaxine extended-release capsules treatment experienced statistically significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

**Table 2: Primary Efficacy Results for Studies in Major Depressive Disorder in Adults (Studies 1 and 2)**

| Study number | Treatment Group | Primary Efficacy Measure: HAM-D Score | | |
|---|---|---|---|---|
| | | LS Mean Change from Baseline | | Placebo Subtracted Difference[b] (95%CI) |
| Study 1 | Venlafaxine extended-release capsules (75 mg[a], 150 mg[a], 225 mg per day) * | 24.5 | -11.7 | -4.45 (-6.66, -2.25) |
| | Placebo | 23.6 | -7.24 | - |
| Study 2 | Venlafaxine extended-release capsules (75 mg[a], 150 mg[a], 225 mg per day) * | 24.5 | -15.11 | -6.40 (-8.45, -4.34) |
| Placebo | Placebo | 24.9 | -8.71 | |

SD: standard deviation; LS Mean: least-squares mean; CI: confidence interval.

[a] Venlafaxine Extended-Release Tablets are only available as 112.5 mg dosage strength.

[b] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.