VENLAFAXINE EXTENDED RELEASE TABLETS (venlafaxine hydrochloride)

INDICATION

- **Venlafaxine Extended Release Tablets are indicated for the treatment of major depressive disorder (MDD) and Social Anxiety Disorder (SAD) also known as Social Phobia, as defined in the DSM-IV-TR.**[1]

PATENTED TECHNOLOGY

- Venlafaxine Extended Release Tablets use the patented Osmodex®† technology.[2]
- This technology uses osmotic pressure to deliver venlafaxine hydrochloride at a controlled rate over 24h.[2]
- This allows for the production of smaller tablets per mg strength, when compared to venlafaxine extended-release capsules.[2]
- The smaller size allows the creation of a unique dosage strength, the single 225 mg tablet.[2]

DOSAGE

- Available in 37.5 mg, 75 mg, 150 mg, and 225 mg dosage strengths, in bottles of either 30 or 90 tablets.[1]
- Titration: MDD patients should start treatment at 37.5 mg or 75 mg/day; daily dose can be increased by 75 mg/day at intervals of ≥4 days (maximum 225 mg per day). If started at 37.5 mg, the patient should be titrated to 75 mg prior to further titration in 75 mg increments.[1]

EFFICACY

- Numerous randomized controlled clinical trials demonstrate the safety and efficacy of Effexor XR®* (venlafaxine hydrochloride) for the treatment of patients with major depressive disorder (MDD) and social anxiety disorder (SAD).[1, 3-5]
- Studies from the approved NDA for Effexor XR® capsules were referenced to support the safety and efficacy of Venlafaxine Extended Release Tablets. These included short-term trials and a longer-term trial in MDD, as well as short-term SAD trials.[6]

SAFETY AND TOLERABILITY *(Please see attached IMPORTANT SAFETY INFORMATION)*

- Safety data was based on the MDD and SAD pivotal trials for Effexor XR®, with additional data obtained in the 4 pivotal bioequivalence studies for Venlafaxine Extended Release Tablets.[1,7-10]
- **Major Depressive Disorder** - Adverse events in short-term studies that occurred in at least 5% of the patients receiving venlafaxine extended-release capsules and at a rate at least twice that of the placebo group were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating.[1]
- **Social Anxiety Disorder** - Adverse events in short-term studies that occurred in at least 5% of the patients receiving venlafaxine extended-release capsules and at a rate at least twice that of the placebo group were asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.[1]
- **Bioequivalence Data**: Among the 4 pivotal bioequivalence studies, Venlafaxine Extended Release Tablets were well-tolerated, with a safety profile similar to that of the reference product, Effexor XR®.[7-10]

DEMONSTRATION OF BIOEQUIVALENCE

- The basis of the clinical development program for Venlafaxine Extended Release Tablets was the demonstration of bioequivalence to Effexor XR® capsules which was determined based on results from four randomized crossover single- and multiple-dose studies under fasting and fed conditions in healthy volunteers. [1, 7-10]
- Equal doses of Venlafaxine Extended Release Tablets and Effexor XR® capsules are bioequivalent when administered under fed conditions.[1, 7-10]
- Due to the difference in dosage form (tablets vs capsules), Venlafaxine Extended Release Tablets are not AB rated to Effexor XR® and are not a generic.

PHARMACOKINETICS AND PHARMACOLOGY

- Steady-state concentrations of venlafaxine and O-desmethylvenlafaxine (ODV) in plasma are attained within 3 days of oral multiple dose therapy. [1]
- After administration of 75 mg Venlafaxine Extended Release Tablets under fed conditions, the mean ± SD apparent elimination half-life for venlafaxine and ODV were 10.7 ± 3.2 hours and 12.5 ± 3.0 hours respectively.
- Administration of 75 mg Venlafaxine ER Tablets under fed conditions resulted in mean ± SD venlafaxine C_{max} of 26.9 ± 13.4 ng/mL and AUC of 1536.3 ± 496.8 ng·hr/mL. T_{max} was 6.3 ± 2.3 hours. ODV mean ± SD C_{max}, AUC, $T_{max.}$
  values were 97.9 ± 29.4 ng/mL, 2926.0 ± 746.1 ng·hr/mL, and 11.6 ± 2.9 hours, respectively.
- Compared with venlafaxine immediate-release tablets, Venlafaxine Extended Release Tablets provides a slower rate of absorption, but the same extent of absorption. [1]

SUMMARY

- Venlafaxine Extended Release Tablets are a bioequivalent reformulation of the effective and well-established Effexor XR® capsules for MDD and SAD. [1]
- Due to the difference in dosage form (tablets vs capsules), Venlafaxine Extended Release Tablets are not AB rated to Effexor XR® and are not a generic.
- The patented Osmodex® technology allows for the production of smaller tablets per mg strength when compared to venlafaxine extended-release capsules, thus making it possible to provide a single 225 mg tablet.[2]
- MDD patients should start treatment at 37.5 mg or 75 mg/day; daily dose can be increased by 75 mg/day at intervals of ≥4 days (maximum 225 mg per day). If started at 37.5 mg, the patient should be titrated to 75 mg prior to further titration in 75 mg increments. [1]
- The Venlafaxine Extended Release Tablets 225 mg dose for MDD patients may simplify the treatment regimen for some patients.

Please see accompanying full Prescribing Information, including complete boxed warning.

References: 1. Venlafaxine Extended Release Tablets Prescribing Information, Osmotica Pharmaceutical, August, 2008. **2.** Haeusler JM.Curr Med Res Opin. 2009 May;25(5):1089-94. Review. **3.** Cunningham LA. Ann Clin Psychiatry. 1997; 9(3):157-164. **4.** Thase ME. *J Clin Psychiatry.* 1997;58(9):393-398. **5.** Rickels K, Mangano R, Khan A. J Clin Psychopharmacol. 2004;24(5):488-496. **6.** U.S. Food and Drug Administration. http://www.fda.gov/cder/foi/appletter/2008/022104s000ltr.pdf. Accessed December 4, 2008. **7.** Data on file. Study 10672001, Upstate Pharma. **8.** Data on file. Study 10572001, Upstate Pharma. **9.** Data on file. Study R04-0776, Upstate Pharma. **10.** Data on file. Study R04-0778, Upstate Pharma.

Important Safety Information

WARNING: Suicidality and Antidepressants
See full Prescribing Information for complete boxed warning.

Increased risk of suicidal thinking and behavior has been reported in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Venlafaxine Extended Release Tablets are not approved for use in pediatric patients.

Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of Major Depressive Disorder (MDD) and Social Anxiety Disorder (SAD). Efficacy of venlafaxine HCl was shown in both short-term trials and a longer-term trial in MDD, and in short-term SAD trials. Venlafaxine Extended Release Tablets are contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).

All patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose. Such monitoring should include daily observation by families and caregivers for emergence of agitation, irritability, unusual changes in behavior, or emergence of suicidality.

Venlafaxine Extended Release Tablets should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping Venlafaxine Extended Release Tablets before starting an MAOI. The development of a potentially life-threatening serotonin syndrome may occur with Venlafaxine Extended Release Tablets, particularly if used concomitantly with serotonergic drugs (including SSRIs, SNRIs, and triptans) or with MAO inhibitors.

Treatment with venlafaxine hydrochloride is associated with sustained hypertension in some patients. Regular blood pressure monitoring is recommended. Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Dosing must be individualized according to the patient's hepatic and renal function status. Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms (generally self-limiting; serious symptoms possible). A gradual reduction in the dose rather than abrupt cessation is recommended.

After treatment with venlafaxine hydrochloride, insomnia and nervousness, activation of mania/hypomania, symptomatic hyponatremia, seizures, abnormal bleeding (most commonly ecchymosis), clinically relevant increases in serum cholesterol, interstitial lung disease and eosinophilic pneumonia have been reported. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures. Measurement of serum cholesterol should be considered during long-term treatment. Patients should be cautioned about the risk of bleeding associated with concomitant use of Venlafaxine Extended Release Tablets and NSAIDs, aspirin, or other drugs that affect coagulation.

Venlafaxine Extended Release Tablets should be used during pregnancy and nursing only if clearly needed due to the potential for serious adverse reactions.

Adverse reactions occurring in short-term studies of major depressive disorder* were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, anorexia), CNS complaints (dizziness, somnolence, abnormal dreams) and sweating. Adverse reactions occurring in short-term studies of social anxiety disorder* were asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

*Occurring in at least 5% of patients receiving venlafaxine extended release capsules and at a rate at least twice that of placebo.

Please see accompanying full Prescribing Information, including complete boxed warning.