EFEXOR® XR (Venlafaxine)

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DESCRIPTION

Active Ingredients
Venlafaxine (INN)

Physical Characteristics
Venlafaxine HCl is a white to off-white crystalline solid.

Pharmacological class, therapeutic class
Serotonin and norepinephrine reuptake inhibitor (SNRI)
Antidepressant
Anxiolytic

Dosage forms and intended routes of administration
Extended-release capsules for oral administration.

Composition and pharmaceutical characteristics
Capsules contain 37.5 mg, 75 mg, or 150 mg venlafaxine (as hydrochloride).

INDICATIONS

Treatment of depression, including depression with associated anxiety.

For prevention of relapse and prevention of recurrence of depression.

Treatment of anxiety or Generalized Anxiety Disorder, including long-term treatment.

Treatment of Social Anxiety Disorder, including long-term treatment.

Treatment of Panic Disorder, including long-term treatment.

Dosage and Administration

It is recommended that Efexor®XR extended-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

With the exception of patients with SAD (see below), patients not responding to the 75 mg/day dose may benefit from dose increases in increments of up to 75 mg/day to a maximum of 225 mg/day. Efexor®XR extended-release dosage increases can be made at intervals of 2 weeks or more, but not less than 4 days.

Patients treated with Efexor® immediate-release tablets may be switched to Efexor®XR extended-release capsules at the nearest equivalent daily dosage. For example, Efexor® immediate-release tablets 37.5 mg twice daily may be switched to Efexor®XR extended-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

- *Major Depressive Disorder:* The recommended starting dose for Efexor®XR extended-release is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day.

  While the recommended dose for moderately depressed patients is up to 225 mg/day for immediate-release Efexor®, more severely depressed patients in one study responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day).

- *Generalized Anxiety Disorder:* The recommended starting dose for Efexor®XR extended-release is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day.

- *Social Anxiety Disorder :* The recommended dose for Efexor®XR extended-release is 75 mg given once daily. There is no evidence that higher doses confer any additional benefit.

- *Panic Disorder:* It is recommended that a dose of 37.5 mg/day of Efexor®XR be used for 7 days. Dosage should then be increased to 75 mg/day. Patients not responding to the 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day.

- *Discontinuing Efexor® (venlafaxine):* Dose tapering is recommended whenever possible when discontinuing Efexor® therapy (see sections 6 &15). In clinical trials with Efexor®XR extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1-week intervals. The period required for tapering may depend on the dose, duration of therapy, and the individual patient.

- *Use in Patients with Renal Impairment:* The total daily dose of Efexor® should be reduced by 25% to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min. The total daily dose of Efexor® should be reduced by 50% in hemodialysis patients. Because of individual variability in clearance in these patients, individualization of dosage may be desirable.

- *Use in Patients with Hepatic Impairment:* The total daily dose of Efexor® should be reduced by 50% in patients with mild to moderate hepatic impairment. Reductions of more than 50% may be appropriate for some patients. Because of individual variability in clearance in these patients, individualization of dosage may be desirable.

- *Use in Children:* There is insufficient experience with the use of Efexor® in patients less than 18 years of age. (See sections *PEDIATRIC USE* and *ADVERSE REACTIONS*.)

- *Use in Elderly Patients:* No specific dosage adjustments of Efexor® are recommended based on patient age.

Contraindications

Hypersensitivity to venlafaxine or any excipients in the formulation. Concomitant use of venlafaxine and any monoamine oxidase inhibitor (MAOI). Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with a MAOI; a shorter interval may be justified in the case of a reversible MAOI (see prescribing information of the reversible MAOI). Venlafaxine must be discontinued for at least 7 days before starting treatment with any MAOI (see section *INTERACTIONS*).

Special Warnings

All patients treated with venlafaxine should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients, and the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose. (See also Sections *PEDIATRIC USE, and ADVERSE REACTIONS*.)

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24 years) with major depression and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.

As with other serotonergic agents, the development of a potentially life threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, may occur with venlafaxine treatment, particularly with concomitant use of other serotonergicdrugs (including SSRIs, SNRIs and triptans), with rugs that impair metabolism of serotonin (including MAOIs), or with atipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). Serotonin syndrome, in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes (see section *INTERACTIONS*).

If concomitant treatment with venlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

Mydriasis may occur in association with venlafaxine. It is recommended that patients with raised intra-ocular pressure or patients at risk for acute narrow angle glaucoma (angle closure glaucoma) be closely monitored.

Precautions

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine. Cases of elevated blood pressure requiring immediate treatment have been reported in postmarketing experience. Measurement of blood pressure is recommended for patients receiving venlafaxine. Pre-existing hypertension should be controlled before treatment with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions.

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression may occur in a small proportion of patients who have received antidepressants, including venlafaxine treatment, dose reduction or discontinuation. As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

Cases of hyponatremia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine, usually in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume depleted, may be at greater risk for this event.

Drugs that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. The risk of skin and mucous membrane bleeding, including gastrointestinal hemorrhage, may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine hydrochloride and weight loss agents is not recommended. Venlafaxine hydrochloride is not indicated for weight loss alone or in combination with other products.

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Discontinuation effects are well known to occur with antidepressants, and it is therefore recommended that the dosage of either formulation of venlafaxine be tapered gradually and the patient monitored (see sections *DOSAGE AND ADMINISTRATION* & *ADVERSE REACTIONS*).

Pregnancy

The safety of venlafaxine in human pregnancy has not been established. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh the possible risks. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalization. Such complications can arise immediately upon delivery.

When venlafaxine was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (on a mg/kg basis) or 2.5 times (on a mg/m^2 basis) the human daily dose of 375 mg of venlafaxine. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m^2 basis.

Lactation

Venlafaxine and O-desmethylvenlafaxine are excreted in human milk; therefore, a decision should be made whether not to breast-feed or to discontinue venlafaxine.

Pediatric Use

Efficacy in patients less than 18 years of age has not been established.

In pediatric clinical trials, the adverse reaction, suicidal ideation, was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol have been observed in children and adolescents (ages 6 to 17 years; see section *ADVERSE REACTIONS*).

Regular measurement of weight and blood pressure is recommended if venlafaxine is used in children and adolescents. Discontinuation of venlafaxine treatment should be considered for children and adolescents who experience a sustained increase in blood pressure. Measurement of serum cholesterol levels should be considered during long term treatment of children and adolescents (see sections *DOSAGE AND ADMINISTRATION & ADVERSE REACTIONS*). Safety in children less than 6 years of age has not been evaluated.

Geriatric Use

No specific dosage adjustments of venlafaxine are recommended based on patient age.

Interactions

- *Monoamine Oxidase Inhibitors (MAOI):* Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of an MAOI (see section *CONTRAINDICATIONS*).

  These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

- *CNS Active Drugs:* The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active drugs.

Serotonin Syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with drugs that impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], or with serotonin precursors (such as tryptophan supplements). (See sections *CONTRAINDICATIONS* and *SPECIAL WARNINGS.)*

If concomitant treatment with venlafaxine and an SSRI, an SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section *SPECIAL WARNINGS*).

- *Indinavir:* A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in C_{max} for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

- *Ethanol:* Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS active drugs, patients should be advised to avoid alcohol consumption while taking venlafaxine.

- *Haloperidol:* A pharmacokinetic study with haloperidol has shown for haloperidol: a 42% decrease in total oral clearance, a 70% increase in AUC, an 88% increase in C_{max}, but no change in half-life. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly.

- *Cimetidine:* At steady-state, cimetidine has been shown to inhibit first-pass metabolism of venlafaxine; however, cimetidine had no effect on the pharmacokinetics of O-desmethylvenlafaxine. The overall pharmacological activity of venlafaxine plus O-desmethylvenlafaxine is expected to increase only slightly in most patients. In the elderly and in patients with hepatic dysfunction this interaction may be more pronounced.

- *Imipramine:* Venlafaxine did not affect the pharmakokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2.5 to 4.5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. This should be taken into account in patients treated with imipramine and venlafaxine concomitantly.

- *Ketoconazole:* A pharmacokinetic study with ketoconazole in extensive (EM) and poor metabolizers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and ODV in subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively. Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects. AUC values for ODV increased by 23% and 33% in EM and PM subjects, respectively. (see section Potential for Other Drugs to Affect Venlafaxine).

- *Metoprolol:* Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to healthy volunteers in a pharmacokinetic interaction study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, hydroxymetoprolol. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. The clinical relevance of this finding in hyperten-sive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethyl venla- faxine.Caution should be exercised with co-administration of venlafaxine and metoprolol.

- *Risperidone:* Venlafaxine increased the risperidone AUC by 32% but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9 hydroxyrisperidone). The clinical significance of this interaction is unknown.

- *Diazepam:* Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

- *Lithium:* The steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine are not affected when lithium is co-administered. Venlafaxine also has no effect on the pharmacokinetics of lithium. (See also subheading above, CNS Active Drugs.)

- *Drugs Highly Bound to Plasma Proteins:* Venlafaxine is not highly bound to plasma proteins (27% bound); therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound is not expected to cause increased free concentrations of the other drug.

- *Drugs Metabolized by Cytochrome P 450 Isoenzymes:* Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2, and CYP2C9 in vitro. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4), diazepam, (CYP3A4 and CYP2C19), and tolbutamide (CYP2C9).

- *Potential for Other Drugs to Affect Venlafaxine:* The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4. Venlafaxine is primarily metabolized to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine.

- *CYP2D6 Inhibitors:* Concomitant use of CYP2D6 inhibitors and venlafaxine may reduce the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of ODV. As venlafaxine and ODV are both pharmacologically active, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

- *CYP3A4 Inhibitors:* Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV (see section *INTERACTIONS-KETOCONAZOLE).* Therefore, caution is advised when combining venlafaxine with a CYP3A4 inhibitor.

- *CYP2D6 and 3A4 Inhibitors:* The concomitant use of venlafaxine with drug treatment(s) that potentially inhibit both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. However, this concomitant use would be expected to increase venlafaxine plasma concentrations. Therefore, caution is advised when combining

- venlafaxine with any agent(s) that produce simultaneous inhibition of these two enzyme systems.

Electroconvulsive Therapy: There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine treatment.

Effects on ACTIVITIES REQUIRING CONCENTRATION AND PERFORMANCE

Venlafaxine did not affect psychomotor, cognitive or complex behavior performance in healthy volunteers. However, any psychoactive drug may impair judgment, thinking, and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.

Abuse and dependence

Clinical studies did not show evidence of drug-seeking behavior, development of tolerance, or dose escalation over time.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability. In a self-administration study, rhesus monkeys have been shown to self-administer venlafaxine intravenously.

Adverse Reactions

Adverse reactions are listed in the Table in CIOMS frequency categories:

Common:	≥1%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%

Frequency unknown: cannot be estimated from the available data

Body System	*Adverse Reactions*
Body As A Whole	
Common:	Asthenia/fatigue, Chills
Uncommon:	Angioedema, Photosensitivity reaction
Very rare:	Anaphylaxis
Cardiovascular	
Common:	Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations
Uncommon:	Hypotension, Postural hypotension, Syncope, Tachycardia
Very rare:	QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)
Digestive	
Common:	Appetite decreased, Constipation, Nausea, Vomiting
Uncommon:	Bruxism, diarrhea
Very rare:	Pancreatitis
Hematological/Lymphatic	
Uncommon:	Ecchymosis, Mucous membrane bleeding, Gastrointestinal hemorrhage
Rare:	Prolonged bleeding time, Thrombocytopenia
Very rare:	Blood dyscrasias, (including agranulocytosis, aplastic anemia, neutropenia and pancytopenia)
Metabolic/Nutritional	
Common:	Serum cholesterol increased (particularly with prolonged administration and possibly with higher doses), Weight loss
Uncommon:	Abnormal liver function tests, Hyponatremia, Weight gain
Rare:	Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
Very rare:	Prolactin increased
Musculoskeletal	
Very rare:	Rhabdomyolysis
Nervous	
Very common:	Headache
Common:	Abnormal dreams, Decreased libido, Dizziness, Dry mouth, Increased muscle tonus, Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation
Uncommon:	Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance
Rare:	Akathisia/psychomotor restlessness, Convulsion, Manic Reaction, Neuroleptic Malignant Syndrome (NMS), Serotonergic Syndrome
Very rare:	Delirium, extrapyramidal reactions (including dystonia and dyskinesia), tardive dyskinesia
Respiratory	
Common:	Yawning
Very rare:	Pulmonary eosinophilia
Skin	
Common:	Sweating, (including Night Sweats)
Uncommon:	Rash, Alopecia
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, Pruritus, Urticaria
Frequency Unknown:	Toxic epidermal necrolysis
Special Senses	
Common:	Abnormality of accomodation, Mydriasis, Visual disturbance
Uncommon:	Altered taste sensation, Tinnitus
Very rare:	Angle closure glaucoma
Urogenital	
Common:	Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction, Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Urinary frequency increased
Uncommon:	Abnormal orgasm (females), Urinary retention
Rare:	Urinary incontinence

The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of treatment; hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paresthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhea, nausea, and vomiting.
In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Pediatric Patients

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see sections *PRECAUTIONS* & *PEDIATRIC USE*).

In pediatric clinical trials, the adverse reaction, suicidal ideation, was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in pediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

Overdosage

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardio-graphic changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear. Prescriptions for venlafaxine should be written for the smallest quantity of drug consistent with good patient management, in order to reduce the risk of overdose.

Recommended Treatment

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.

Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients.
Administration of activated charcoal may also limit drug absorption.

Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

No specific antidotes for venlafaxine are known.

Mode of Action

Venlafaxine and its active metabolite, O-desmethylvenla-faxine, are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. The antidepressant activity of venlafaxine is thought to be associated with potentiation of neurotrans-mitter activity in histaminergic, or 1-adrenergic receptors in vitro. Activity at these receptors is potentially associated with various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In preclinical rodent models, venlafaxine demonstrated activity predictive of antidepressant and anxiolytic actions, and cognitive enhancing properties.the central nervous system (CNS). Venlafaxine and O-desmethylvenlafaxine have no significant affinity for muscarinic,

Pharmacodynamics, clinical efficacy

Depression

The efficacy of venlafaxine extended-release capsules as a treatment for depression, including depression with associated anxiety, was established in two placebo-controlled, short-term studies. Populations in both trials consisted of outpatients meeting DSM III-R or DSM-IV criteria for major depression.

The first study compared extended-release venlafaxine 75 to 150 mg/day, immediate-release venlafaxine 75 to 150 mg/day, and placebo for 12 weeks. Extended-release venlafaxine showed significant advantage over placebo starting at week 2 of treatment on the Hamilton Rating Score for Depression (HAM-D) total and HAM-D Depressed Mood Item, at week 3 on the Montgomery-Asberg Depression Rating Scale (MADRS) total, and at week 4 on the Clinical Global Impressions (CGI) Severity of Illness Scale. All advantages were maintained through the end of treatment. Extended-release venlafaxine also showed significant advantage over immediate-release venlafaxine at weeks 8 and 12 on the HAM-D total and CGI Severity of Illness Scale and at week 12 for all efficacy variables.

The second study compared treatment with extended-release venlafaxine 75 to 225 mg/day and placebo for up to 8 weeks. Sustained statistical improvement over placebo was seen beginning at week 2 for the CGI Severity of Illness scale, beginning at week 4 for the HAM-D total and MADRS total, and beginning at week 3 for the HAM-D Depressed Mood Item.

Generalized Anxiety Disorder

The efficacy of venlafaxine extended-release capsules as a treatment for Generalized Anxiety Disorder (GAD) was established in two short-term (8-week), placebo-controlled, fixed-dose studies, one long-term (6-month), placebo-controlled, fixed-dose study, and one long-term (6-month), placebo-controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD. One short-term study evaluating extended-release venlafaxine doses of 75,

150, and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, placebo for the 75 and 150 mg/day doses, these doses were not as consistently effective as the highest dose.

A second short-term study evaluating extended-release venlafaxine doses of 75 and 150 mg/day and placebo showed that both doses were more effective than placebo on some of these same outcomes, however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. Two long-term (6-month studies), one with extended-release venlafaxine doses of 37.5, 75, and 150 mg/day and the other evaluating doses of 75 to 225 mg/day, showed that 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 after short-term (week 8) and the long-term (month 6) treatment.both the HAM-A anxiety and tension items, and the CGI scale. While there was also evidence for superiority over

- *Absorption:* At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. In single-dose studies with 25 to 150 mg of immediate-release venlafaxine, mean peak plasma concentrations (C_{max}) range respectively from 37 to 163 ng/mL and are attained within 2.1 to 2.4 hours (t_{max}). Following the administration of venlafaxine extended-release capsules, peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 5.5 hours and 9 hours, respectively. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine occur in 2 and 3 hours, respectively. Venlafaxine extended-release capsules and venlafaxine immediate-release tablets are associated with a similar extent of absorption.

- *Distribution:* Steady-state concentrations of both venlafaxine and O-desmethylvenlafaxine in plasma are attained within 3 days of multiple-dose therapy of immediate-release venlafaxine. Both show linear kinetics over a dose range of 75 to 450mg/day when administered every 8 hours. Venlafaxine and O-desmethylvenlafaxine are approximately 27% and 30% bound to human plasma proteins, respectively. Since this binding is independent of respective drug concentrations up to 2,215 and 500 ng/mL, both venlafaxine and O-desmethylvenlafaxine have low potential for involvement in significant drug-drug interactions involving drug displacement from serum proteins. The volume of distribution for venlafaxine at steady-state is 4.4 ± 1.9 L/kg following intravenous administration.

- *Metabolism:* Venlafaxine undergoes extensive hepatic metabolism. In vitro and in vivo studies indicate that venlafaxine is biotransformed to its major active metabolite, O-desmethylvenlafaxine, by the P450 isoenzyme CYP2D6. In vitro and in vivo studies indicate that venlafaxine is metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4.

  Although the relative activity of CYP2D6 may differ among patients, related modification of the venlafaxine dosage regimen is not required. Drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and O-desmethylvenlafaxine were comparable following administration of equal daily doses of venlafaxine as b.i.d. or t.i.d. regimens of immediate-release venlafaxine.

- *Elimination:* Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated O-desmethylvenlafaxine (29%), conjugated O-desmethylvenlafaxine (26%), or other minor inactive metabolites (27%).

  Effects of Food: Food has no significant effect on the absorption of venlafaxine or the formation of O-desmethylvenlafaxine.

  Patients with Hepatic Impairment: The pharmacokinetic disposition of venlafaxine and O-desmethylvenlafaxine are significantly altered in some patients with compensated hepatic cirrhosis (moderate hepatic impairment) following oral administration of single-dose venlafaxine.
  In hepatically-impaired patients, mean plasma clearance of venlafaxine and O-desmethylvenlafaxine are reduced approximately 30 to 33% and mean elimination half-lives are prolonged 2-fold or more compared to normal subjects.

  In a second study, venlafaxine was administered orally and intravenously in normal subjects (n = 21), and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects (mildly and moderately hepatically-impaired, respectively).
  Oral bioavailability approximately doubled for hepatically impaired subjects compared to normal subjects.
  In hepatically-impaired subjects, venlafaxine oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half compared to normal subjects. In hepatically-impaired subjects, ODV oral elimination half-life was prolonged by about 40% while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted.

- *Patients with Renal Impairment:* Venlafaxine and O-desmethylvenlafaxine elimination half-lives increase with the degree of impairment in renal function. Elimination half-life increased approximately 1.5-fold in patients with moderate renal impairment and approximately 2.5-fold and 3-fold in patients with end stage renal disease.

- *Age and Gender Studies:* A population pharmacokinetic analysis of 404 immediate-release venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or O-desmethylvenlafaxine were unaltered by age or gender differences.

Preclinical safety Data

- *Carcinogenicity:* Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of O-desmethylvenlafaxine were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

- *Mutagenicity:* Venlafaxine and O-desmethylvenlafaxine were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the in vitro BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the in vivo chromosomal aberration assay in rat bone marrow. O-desmethylvenlafaxine was not clastogenic in the in vitro Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow.

- *Impairment of Fertility:* Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or of up to 2 times on a mg/m^2 basis.

  Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This ODV exposure was approximately 2 to 3 times that of a human venlafaxine dose of 225 mg/day. The human relevance of this finding is unknown.

- *Teratogenicity:* Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the human dose of 375 mg/day of venlafaxine (on a mg/kg basis), or 2.5 times (rat) and 4 times (rabbit) the human dose of 375 mg/day of venlafaxine (on a mg/m^2 basis).

Storage

Protect Efexor®XR extended-release capsules from light, heat and moisture.

Other Information

The extended-release formulation of Efexor®XR contains spheroids, which release the drug slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.

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