VENLAFAXINE HCl

EFFEXOR® XR EXTENDED RELEASE CAPSULES

Brief Summary

See package insert for full prescribing information.

Indications and Usage: Effexor XR is indicated for the treatment of depression and for the treatment of Generalized Anxiety Disorder (GAD).

Contraindications: Effexor XR is contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see "**Warnings**").

Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS—**Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.**

SUSTAINED HYPERTENSION—Venlafaxine is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg per day of Effexor XR in premarketing depression studies, 3% experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 75-225 mg per day of Effexor XR in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension. Experience with immediate release venlafaxine showed that sustained hypertension was dose related, increasing from 3-7% at 100-300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of Effexor XR >300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses. In premarketing depression and GAD studies, 0.7% and 0.4% of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. It is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.

Precautions: GENERAL—*Insomnia and Nervousness*: Treatment-emergent insomnia and nervousness have been reported for patients treated with Effexor XR. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in Phase 3 depression studies. In Phase 3 GAD trials, insomnia and nervousness led to drug discontinuation in 5% and 3%, respectively, of the patients treated with Effexor XR. *Changes in Appetite/Weight*: Treatment-emergent anorexia has been reported in short-term depression and GAD studies. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 0% of the placebo-treated patients in placebo-controlled GAD trials. *Activation of Mania/Hypomania*: Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania. *Hyponatremia*: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics. *Mydriasis*: Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma should be monitored. *Seizures*: No seizures occurred among Effexor XR-treated patients in short-term trials. In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine-treated patients. Use Effexor XR cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. *Skin and Mucous Membrane Bleeding*: The risk of skin and mucous membrane bleeding may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding at these sites. *Suicide*: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same precautions observed when treating patients with depression should be observed when treating patients with GAD. *Use in Patients With Concomitant Illness*: Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. In short-term depression studies electrocardiographic changes in corrected QT interval (QTc) for Effexor XR-treated patients showed a mean increase of 4.7 msec. In these same trials, the mean change from baseline heart rate for Effexor XR-treated patients was 4 beats per minute. In short-term GAD studies, mean changes in QTc for Effexor XR-treated patients did not differ significantly from placebo. The mean change from baseline heart rate for Effexor XR-treated patients in anxiety studies was 3 beats per minute. The clinical significance of these changes is unknown. In patients with renal impairment (GFR=10-70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients.

INFORMATION FOR PATIENTS—Clinical studies in healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to 1) notify their physician if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) inform physician about other prescription or over the counter medications they are taking or plan to take; 3) avoid alcohol while taking Effexor XR; 4) notify their physician if they develop a rash, hives, or related allergic phenomena.

LABORATORY TESTS: There are no specific laboratory tests recommended.

DRUG INTERACTIONS—*Cimetidine*: Use with caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly.

Haloperidol: Venlafaxine (150 mg/day) decreased total oral-dose clearance (Cl/F) of haloperidol which resulted in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged.

Drugs Inhibiting Cytochrome P4502D6 Metabolism: Venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. However, since the composite plasma levels of venlafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

The concomitant use of venlafaxine with a drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.

Drugs Metabolized by Cytochrome P450 Isoenzymes: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4 (*in vitro* and *in vivo*), CYP2C9 (*in vitro*), or CYP2C19 (*in vivo*).

Imipramine—Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by 2.5-4.5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown. Risperidone—Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). Indinavir—In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800-mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown. *Monoamine Oxidase Inhibitors*: See **"Contraindications"** and **"Warnings."**

CNS-Active Drugs: Use of venlafaxine with CNS-active drugs has not been systematically evaluated; use caution when administering Effexor XR with such drugs.

Postmarketing Spontaneous Drug Interaction Reports: See **"ADVERSE REACTIONS," "Postmarketing Reports."**

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY—*Carcinogenesis*: There was no increase in tumors in 18-month studies in mice given up to 120 mg/kg/day [1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis] or in 24-month studies in rats given up to 120 mg/kg/day.

Mutagenesis: Venlafaxine and ODV 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 not clastogenic in several assays. ODV elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis.

PREGNANCY—*Teratogenic Effects—Pregnancy Category C*. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, 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. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed.

LABOR, DELIVERY, NURSING—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE—Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE—Approximately 4% and 3% of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase depression studies, 12% were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

Adverse Reactions: ASSOCIATED WITH DISCONTINUATION OF TREATMENT—Approximately 11% and 23% of Effexor XR patients in placebo-controlled clinical depression and GAD trials, respectively, discontinued treatment due to an adverse event. The most common events leading to discontinuation in at least 1% of patients and at least twice that of placebo in depression trials included: nausea, anorexia, dry mouth, dizziness, insomnia, and somnolence; in U.S. placebo-controlled depression trials included: hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, and abnormal (mostly delayed) ejaculation; in GAD trials included: headache, asthenia, vasodilation, nausea, anorexia, dry mouth, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, and abnormal vision. INCIDENCE IN CONTROLLED TRIALS—*Commonly Observed Adverse Events in Controlled Clinical Trials*: The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled depression trials (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): nausea (31% vs. 12%), dizziness (20% vs. 9%), somnolence (17% vs. 8%), abnormal ejaculation (16% vs. <1%), sweating (14% vs. 3%), dry mouth (12% vs. 6%), nervousness (10% vs. 5%), anorexia (8% vs. 4%), abnormal dreams (7% vs. 2%), and tremor (5% vs. 2%). In U.S. placebo-controlled depression trials, the following were also reported with an incidence of at least 5% and at least twice that for placebo: impotence, anorgasmia, decreased libido, constipation, flatulence, insomnia, nervousness, tremor, abnormal vision, hypertension, vasodilation, and yawning. The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled GAD trials (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): nausea (43% vs. 11%), dry mouth (23% vs. 5%), insomnia (22% vs. 11%), abnormal ejaculation (17% vs. 0%), anorexia (13% vs. 2%), constipation (12% vs. 5%), nervousness (12% vs. 5%), sweating (11% vs. <1%), abnormal vision (8% vs. 0%), yawn (6% vs. <1%), impotence (6% vs. 1%), decreased libido (6% vs. 2%), vasodilation (6% vs. 2%), vomiting (6% vs. 2%).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients: The following occurred in short-term, placebo-controlled depression trials (up to 12 weeks) with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia. **Cardiovascular:** vasodilatation, hypertension. **Digestive:** nausea, constipation, anorexia, vomiting, flatulence. **Metabolic/Nutritional:** weight loss. **Nervous System:** dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, paresthesia, libido decreased, agitation. **Respiratory System:** pharyngitis, yawn. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, anorgasmia (female). The following occurred in short-term, placebo-controlled GAD trials (up to 8 weeks), with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia, infection, abdominal pain, fever, neck pain, chills. **Cardiovascular:** vasodilatation, tachycardia. **Digestive:** nausea, anorexia, diarrhea, constipation, vomiting, flatulence. **Musculoskeletal System:** myalgia. **Nervous System:** dry mouth, insomnia, dizziness, somnolence, nervousness, libido decreased, abnormal dreams, tremor, paresthesia, thinking abnormal, trismus, twitching. **Respiratory System:** rhinitis, yawn, cough increased. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, dysmenorrhea, orgasmic dysfunction (female), urinary frequency.

Vital Sign Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the **"Sustained Hypertension"** section of **"Warnings"** for effects on blood pressure.)

Laboratory Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in serum cholesterol concentration of about 1.5 mg/dL and 2.5 mg/dL, respectively; clinical significance is unknown. Patients treated with Effexor tablets for at least 3 months in 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL. This increase was duration dependent and tended to be greater with higher doses. An increase in serum cholesterol from baseline by ≥ 50 mg/dL and to values > 260 mg/dL, at any time after baseline, has been recorded in 8.1% of patients.

ECG Changes: (See the *"Use in Patients With Concomitant Illnesses"* section of **"Precautions"**.)

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF EFFEXOR AND EFFEXOR XR—During premarketing assessment, multiple doses of Effexor XR or Effexor were administered to 4174 patients, and the following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = fewer than 1/1000 patients. It is important to emphasize that although the events occurred during treatment with venlafaxine, they were not necessarily caused by it.

Body as a whole - **Frequent:** chest pain substernal; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; **Rare:** appendicitis, carcinoma, cellulitis, withdrawal syndrome. Cardiovascular system - **Frequent:** migraine, postural hypotension; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mitral valve disorder, mucocutaneous hemorrhage, myocardial infarct, pallor. Digestive system - **Frequent:** eructation, increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, stomatitis, mouth ulceration; **Rare:** cheilitis, cholecystitis, cholelithiasis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, oral moniliasis, proctitis, increased salivation, soft stools, tongue discoloration. Endocrine system - **Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, cyanosis, eosinophilia, lymphocytosis. Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, glycosuria, hypercholesteremia, hyperglycemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, dehydration, gout, hemochromatosis, hypercalcinuria, hyperkalemia, hyperlipemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia. Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture. Nervous system - **Frequent:** amnesia, confusion, depersonalization, emotional lability, hypesthesia, vertigo; **Infrequent:** apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, seizure, abnormal speech, stupor; **Rare:** akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barré Syndrome, hypokinesia, neuritis, nystagmus, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. Respiratory system - **Frequent:** dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, pleurisy, pulmonary embolus, sleep apnea. Skin and appendages - **Frequent:** rash, pruritus; **Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythremia nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - **Frequent:** metrorrhagia,* prostatitis,* urination impaired, vaginitis*; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, female lactation,* leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare:** abortion,* anuria, breast engorgement, breast enlargement, fibrocystic breast, calcium crystalluria, cervicitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.* (*Based on the number of men and women as appropriate.)

Postmarketing Reports: Voluntary reports of other adverse events temporally associated with the use of Effexor (the immediate release form of venlafaxine) that have been received since market introduction and that may have no causal relationship with the use of Effexor include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities (such as atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia), epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), fatigue, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of Effexor or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

Drug Abuse and Dependence: Effexor® XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of venlafaxine misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: In premarketing evaluation of Effexor XR for depression, there were 2 reports of acute overdosage (6 g of Effexor XR with 2.5 mg of lorazepam, and 2.85 g of Effexor XR). Both recovered without sequelae. In premarketing evaluation of Effexor, there were 14 reports of acute overdosage (highest dose was 6.75 g). All patients recovered without sequelae. Most patients reported no symptoms. Symptoms observed included somnolence, generalized convulsions, prolongation of QTc to 500 msec (compared with 405 msec at baseline) in one case, and mild sinus tachycardia. In premarketing evaluation of Effexor XR for GAD, there were 2 reports of acute overdosage (0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem, and 1.2 g of Effexor XR). Both recovered without sequelae. In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported.

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference®* (PDR).

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **"Contraindications"** and **"Warnings"**).

Please consult full prescribing information for detailed dosing instructions.

This brief summary is based on the circular 5044-5, revised April 14, 2000.

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

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In Depression or Generalized Anxiety Disorder

The goal is recovery

- Working on both serotonin and norepinephrine, EFFEXOR XR has been shown to offer more patients the ability to achieve recovery.[1]

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EFFEXOR® XR EXTENDED RELEASE CAPSULES

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Please see brief summary of Prescribing Information on adjacent page.

The efficacy and safety of EFFEXOR XR for pediatric use have not been established.

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR 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 EFFEXOR XR before starting an MAOI.

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.

Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. Less than 1% discontinued treatment because of elevated BP. Regular BP monitoring is recommended.

Reference: 1. Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa.

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