VENLAFAXINE HCl
EFFEXOR® XR
EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information. **CONTRAINDICATIONS**: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. **WARNINGS**: **Potential for Interaction with Monoamine Oxidase Inhibitors—Adverse reactions, some serious, have been reported in patients who were recently discontinued from an MAOI and started on venlafaxine, or who recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. It is recommended that Effexor XR 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 (BP) in some patients. Experience with immediate release venlafaxine showed that sustained hypertension was dose related. It is recommended that patients receiving Effexor XR have regular monitoring of BP. For patients who experience a sustained increase in BP either dose reduction or discontinuation should be considered. **PRECAUTIONS**: **General**—***Insomnia and Nervousness:*** Treatment-emergent insomnia and nervousness have been reported. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients in Phase 3 depression studies. In Phase 3 Generalized Anxiety Disorder (GAD) trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of patients. ***Changes in Appetite/Weight:*** Treatment-emergent anorexia has been reported. A loss of 5% or more of body weight occurred in 7% of patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of 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; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma should be monitored. ***Seizures:*** 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. ***Abnormal Bleeding:*** There have been reports of abnormal bleeding (most commonly ecchymosis). ***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 should be observed when treating patients with GAD. ***Use in Patients With Concomitant Illness:*** 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) showed a mean increase of 4.7 msec. and the mean change from baseline heart rate was 4 beats per minute. In GAD studies, mean changes in QTc did not differ significantly from placebo and the mean change from baseline heart rate was 3 beats per minute. In a flexible-dose study with immediate release Effexor (mean dose >300 mg/day), patients had a mean increase in heart rate of 8.5 beats per minute. Caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent MI). In patients with renal impairment 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**—Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—There are no specific laboratory tests recommended. **Drug Interactions**—***Alcohol:*** A single dose of ethanol had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine:*** Use with caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam:*** A single dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV. Venlafaxine did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol:*** Venlafaxine decreased total oral-dose clearance 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, ODV, via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. 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. 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, CYP2C9 (in vitro), or CYP2C19. ***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. ***Risperidone:*** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. 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 resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. ***MAOIs:*** See "Contraindications" and "Warnings." ***CNS-Active Drugs:*** Caution is advised if the concomitant administration of venlafaxine and CNS-active drugs is required. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis:*** There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. ***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. ***Nonteratogenic Effects.*** If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. **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 6% of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, 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. 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***—The most common events leading to discontinuation in depression and GAD trials included: nausea, anorexia, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for Depression and GAD***—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, hypertonia, paresthesia, libido decreased, agitation. Respiratory System: pharyngitis, yawn. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, anorgasmia (female). ***Vital Sign Changes:*** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the "Sustained Hypertension" section of "Warnings.") ***Laboratory Changes:*** Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled depression trials was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively. Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL. This increase was duration dependent over the 12-month study period 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***—N=5079. "Frequent"= events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, cardiovascular disorder (mitral valve and circulatory disturbance), 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, oral moniliasis, stomatitis, mouth ulceration; Rare: cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, 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, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, 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, thinking abnormal, trismus, vertigo; Infrequent: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, twitching; Rare: akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, libido increased, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, 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: erythema nodosum, exfoliative dermatitis, *lichenoid dermatitis, hair discoloration, skin discoloration*, furunculosis, hirsutism, leukoderma, petechial rash, 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, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, chromatopsia, conjunctival edema, deafness, exophthalmos, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: dysuria, metrorrhagia,* prostatic disorder *(prostatitis and enlarged prostate),* urination impaired, vaginitis*; Infrequent: albuminuria, amenorrhea,* cystitis, hematuria, leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; Rare: abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* 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**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), 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), night sweats, pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of venlafaxine 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 misuse or abuse. **OVERDOSAGE**: 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). **DOSAGE AND ADMINISTRATION:** Please consult full prescribing information for detailed dosing instructions. **Discontinuing Effexor XR**—When discontinuing Effexor XR, the dose should be tapered gradually, based upon the dose, duration of therapy and the individual patient. Discontinuation symptoms reported include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo and vomiting. **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.") This brief summary is based on the circular CI 7509-1, revised September 12, 2001.

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Something extra

...1/3 more patients got their life back

In a pooled analysis of over 2,000 patients, against leading SSRIs (fluoxetine, paroxetine, fluvoxamine), EFFEXOR XR/EFFEXOR offered something extra—**remission* of depression in 1/3 more patients.**[1] Remission of symptoms is a first step on the road to recovery.[2]

***Remission is defined as minimal or no symptoms (HAM-D ≤7).**[1]

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.

Patients should not be abruptly discontinued from antidepressant medication, including EFFEXOR XR. See the Dosage and Administration section of the Prescribing Information.

References: 1. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry.* 2001;178:234-241.
2. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry.* 1991;52(5, suppl):28-34.

Please see brief summary of Prescribing Information on adjacent page.

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Indicated for Depression and Generalized Anxiety Disorder

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https://doi.org/10.1017/S1092852900022197 Published online by Cambridge University Press