HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EFFEXOR XR safely and effectively. See full prescribing information for EFFEXOR XR.

EFFEXOR XR® (venlafaxine Extended-Release) Capsules
Initial U.S. Approval: 1997

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)**
- **Effexor XR is not approved for use in pediatric patients (8.4)**

INDICATIONS AND USAGE

Effexor XR is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of:
- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Social Anxiety Disorder (SAD)
- Panic Disorder (PD)

DOSAGE AND ADMINISTRATION

Indication	Starting Dose	Target Dose	Maximum Dose
MDD (2.1)	37.5 -75 mg/day	75 mg/day	225 mg/day
GAD (2.2)	37.5 -75 mg/day	75 mg/day	225 mg/day
SAD (2.3)	75 mg/day	75 mg/day	75 mg/day
PD (2.4)	37.5 mg/day	75 mg/day	225 mg/day

- Take once daily with food (2). Capsules should be taken whole; do not divide, crush, chew, or dissolve (2).
- When discontinuing treatment, reduce the dose gradually (2.8, 5.7).
- Renal impairment: reduce the total daily dose by 25% to 50% in patients with renal impairment. Reduce the total daily dose by 50% or more in patients undergoing dialysis or with severe renal impairment (2.6).
- Hepatic impairment: reduce the daily dose by 50% in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment or hepatic cirrhosis, it may be necessary to reduce the dose by more than 50% (2.6).

DOSAGE FORMS AND STRENGTHS

- Effexor XR capsules are available as 37.5 mg, 75 mg and 150 mg strengths (3).
- Each capsule contains venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg or 150 mg of venlafaxine (3).

CONTRAINDICATIONS

- Hypersensitivity to venlafaxine hydrochloride, desvenlafaxine succinate, or any excipients in the Effexor XR formulation (4.1).
- Do not use with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping Effexor XR before starting an MAOI, because of the risk of serotonin syndrome (4.2, 5.2, 7.3).

WARNINGS AND PRECAUTIONS

- **Clinical Worsening/Suicide Risk:** Monitor for clinical worsening and suicide risk (5.1).
- **Serotonin Syndrome:** Risk increases with concomitant use of other serotonergic drugs. Discontinue Effexor XR and initiate supportive treatment if serotonin syndrome occurs (4.2, 5.2, 7.3).
- **Elevations in Blood Pressure:** Control hypertension before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- **Abnormal Bleeding:** Effexor XR may increase risk of bleeding events. Caution patients about the risk of bleeding associated with the concomitant use of Effexor XR and NSAIDs, aspirin, or other drugs that affect coagulation (5.4).
- **Angle Closure Glaucoma:** Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.5).
- **Activation of Mania/Hypomania:** Use cautiously in patients with bipolar disorder. Caution patients about the risk of activation of mania/hypomania (5.6).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo): nausea, somnolence, dry mouth, sweating, abnormal ejaculation, anorexia, constipation, erectile dysfunction, and libido decreased (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- **Serotonergic Drugs (e.g., MAOIs, triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort):** Potential for serotonin syndrome. Careful patient observation is advised (4.2, 5.2, 7.3).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [*see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy monitor closely for clinical worsening and emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [*see Warnings and Precautions (5.1) and Patient Counseling Information (17)*].

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

Effexor XR (venlafaxine hydrochloride) extended-release capsules are indicated for the treatment of major depressive disorder (MDD). Efficacy was established in three short-term (4, 8, and 12 weeks) and two long-term, maintenance trials.

1.2 Generalized Anxiety Disorder

Effexor XR is indicated for the treatment of Generalized Anxiety Disorder (GAD). Efficacy was established in two 8-week and two 26-week placebo-controlled trials.

1.3 Social Anxiety Disorder

Effexor XR is indicated for the treatment of Social Anxiety Disorder (SAD), also known as social phobia. Efficacy was established in four 12-week and one 26-week, placebo-controlled trials.

1.4 Panic Disorder

Effexor XR is indicated for the treatment of Panic Disorder (PD), with or without agoraphobia. Efficacy was established in two 12-week placebo-controlled trials.

2 DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food, either in the morning or in the evening at approximately the same time each day [*see Clinical Pharmacology (12.3)*]. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets (spheroids).

2.1 Major Depressive Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg per day, administered in a single dose. For some patients, it may be desirable to start at 37.5 mg per day for 4 to 7 days to allow new patients to adjust to the medication before increasing to 75 mg per day. Patients not responding to the initial 75 mg per day dose may benefit from dose increases to a maximum of 225 mg per day. Dose increases should be in increments of up to 75 mg per day, as needed, and should be made at intervals of not less than 4 days, since steady-state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4 [*see Clinical Pharmacology (12.3)*]. In the clinical studies establishing efficacy, upward titration was permitted at intervals of 2 weeks or more.

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It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg per day for Effexor (immediate-release), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg per day (range of 150 to 375 mg per day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg per day is very limited.

2.2 Generalized Anxiety Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg per day, administered in a single dose. For some patients, it may be desirable to start at 37.5 mg per day for 4 to 7 days to allow new patients to adjust to the medication before increasing to 75 mg per day. Patients not responding to the initial 75 mg per day dose may benefit from dose increases to a maximum of 225 mg per day. Dose increases should be in increments of up to 75 mg per day, as needed, and should be made at intervals of not less than 4 days, since steady-state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4 [*see Clinical Pharmacology (12.3)*].

2.3 Social Anxiety Disorder (Social Phobia)

The recommended dose is 75 mg per day, administered in a single dose. There was no evidence that higher doses confer any additional benefit.

2.4 Panic Disorder

The recommended starting dose is 37.5 mg per day of Effexor XR for 7 days. Patients not responding to 75 mg per day may benefit from dose increases to a maximum of approximately 225 mg per day. Dose increases should be in increments of up to 75 mg per day, as needed, and should be made at intervals of not less than 7 days.

2.5 Switching Patients from Effexor Tablets

Depressed patients who are currently being treated at a therapeutic dose with Effexor (immediate release) may be switched to Effexor XR at the nearest equivalent dose (mg per day), e.g., 37.5 mg venlafaxine twice a day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

2.6 Specific Populations

Patients with Hepatic Impairment

The total daily dose should be reduced by 50% in patients with mild (Child-Pugh=5-6) to moderate (Child-Pugh=7-9) hepatic impairment. In patients with severe hepatic impairment (Child-Pugh=10-15) or hepatic cirrhosis, it may be necessary to reduce the dose by 50% or more [*See Use in Specific Populations (8.7)*].

Patients with Renal Impairment

The total daily dose should be reduced by 25% to 50% in patients with mild (CLcr= 60-89 mL/min) or moderate (CLcr= 30-59 mL/min) renal impairment. In patients undergoing hemodialysis or with severe renal impairment (CLcr < 30 mL/min), the total daily dose should be reduced by 50% or more. Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients [*see Use in Specific Populations (8.7)*].

2.7 Maintenance Treatment

There is no body of evidence available from controlled studies to indicate how long patients with MDD, GAD, SAD, or PD should be treated with Effexor XR.

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It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Effexor XR/Effexor have demonstrated continuation of response in clinical studies up to 52 weeks, at the same dose at which patients responded during the initial treatment [*see Clinical Studies (14.1)*]. It is not known whether or not the dose of Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with GAD and SAD, Effexor XR has been shown to be effective in 6-month clinical studies. The need for continuing medication in patients with GAD and SAD who improve with Effexor XR treatment should be periodically reassessed.

In a clinical study for PD, patients continuing Effexor XR at the same dose at which they responded during the initial 12 weeks of treatment experienced a statistically significantly longer time to relapse than patients randomized to placebo [*see Clinical Studies (14.4)*]. The need for continuing medication in patients with PD who improve with Effexor XR treatment should be periodically reassessed.

2.8 Discontinuing Effexor XR

A gradual reduction in the dose, rather than abrupt cessation, is recommended whenever possible. In clinical studies with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at one-week intervals. Individualization of tapering may be necessary [*see Warnings and Precautions (5.7)*].

2.9 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI (intended to treat psychiatric disorders) and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI intended to treat psychiatric disorders [*see Contraindications (4.2), Warnings and Precautions (5.2), and Drug Interactions (7.2)*].

Use of Effexor XR with other MAOIs such as Linezolid or Intravenous Methylene Blue

Do not start Effexor XR in a patient who is being treated with linezolid or intravenous methylene blue, because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization should be considered [*see Contraindications 4.2)*].

In some cases, a patient already receiving Effexor XR therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Effexor XR should be stopped promptly, and linezolid or intravenous methylene blue can be administered. Monitor the patient for symptoms of serotonin syndrome for 7 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Effexor XR can be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [*see Warnings and Precautions (5.2)*].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg concomitantly with Effexor XR is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

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3 DOSAGE FORMS AND STRENGTHS

Effexor XR® (venlafaxine hydrochloride) extended-release capsules are available in the following strengths:

- 37.5 mg capsules (grey cap/peach body with “W” and “Effexor XR” on the cap and “37.5” on the body)
- 75 mg capsules (peach cap and body with “W” and “Effexor XR” on the cap and “75” on the body)
- 150 mg capsules (dark orange cap and body with “W” and “Effexor XR” on the cap and “150” on the body)

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Hypersensitivity to venlafaxine hydrochloride, desvenlafaxine succinate or to any excipients in the formulation

4.2 Concomitant Use with Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs (intended to treat psychiatric disorders) concomitantly with Effexor XR or within 7 days of discontinuing treatment with Effexor XR is contraindicated because of an increased risk of serotonin syndrome. The use of Effexor XR within 14 days of discontinuing treatment with an MAOI (intended to treat psychiatric disorders) is also contraindicated *[see Dosage and Administration (2.9), Warnings and Precautions (5.2), and Drug Interactions (7.2)]*.

Starting Effexor XR in a patient who is being treated with an MAOI such as linezolid or intravenous methylene blue is also contraindicated, because of an increased risk of serotonin syndrome [*see Dosage and Administration (2.9), Warnings and Precautions (5.2), and Drug Interactions (7.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD 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 age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs

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studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1: Difference in the Number of Cases of Suicidality per 1,000 Patients Treated versus Placebo

Age Range	Increases Compared to Placebo
< 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD, as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.7) and Dosage and Administration (2.8)*].

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers**.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor XR is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Effexor XR alone, but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's wort) and with drugs that impair metabolism of serotonin in particular, MAOIs, both those intended to treat psychiatric disorders and others, such as linezolid or intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, coma) autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis, flushing, and dizziness), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination); seizures and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Effexor XR with MAOIs (intended to treat psychiatric disorders) is contraindicated. Effexor XR should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking Effexor XR. Effexor XR should be discontinued before initiating treatment with the MAOI [*see Contraindications (4.2), Dosage and Administration (2.6), and Drug Interactions (7.3)*].

If concomitant use of Effexor XR with other serotonergic drugs (e.g., triptans, tricyclic antidepressants, mirtazapine, fentanyl, lithium, tramadol, buspirone, tryptophan, or St. John's wort) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Drug Interactions (7.3)*]. Patients should be made aware of the potential risk of serotonin syndrome. Treatment with Effexor XR and any concomitant serotonergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

5.3 Elevations in Blood Pressure

In controlled trials, there were dose-related increases in systolic and diastolic blood pressure, as well as cases of sustained hypertension *[see Adverse Reactions (6.2)]*.

Monitor blood pressure before initiating treatment with Effexor XR and regularly during treatment. Control pre-existing hypertension before initiating treatment with Effexor XR. Use caution in treating patients with pre-existing hypertension or cardiovascular or cerebrovascular conditions that might be compromised by increases in blood pressure. Sustained blood pressure elevation can lead to adverse outcomes. Cases of elevated blood pressure requiring immediate treatment have been reported with

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Effexor XR. Consider dose reduction or discontinuation of treatment for patients who experience a sustained increase in blood pressure.

Across all clinical studies with Effexor, 1.4% of patients in the Effexor XR treated groups experienced a ≥15 mm Hg increase in supine diastolic blood pressure (SDBP) ≥ 105 mm Hg, compared to 0.9% of patients in the placebo groups. Similarly, 1% of patients in the Effexor XR treated groups experienced a ≥ 20 mm Hg increase in supine systolic blood pressure (SSBP) with blood pressure ≥ 180 mm Hg, compared to 0.3% of patients in the placebo groups [*see Table 10 in Adverse Reactions (6.2)*]. Effexor XR treatment was associated with sustained hypertension (defined as treatment-emergent SDBP ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for three consecutive on-therapy visits [*see Table 11 in Adverse Reactions (6.2)*]. An insufficient number of patients received mean doses of Effexor XR over 300 mg per day in clinical studies to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

5.4 Abnormal Bleeding

SSRIs and SNRIs, including Effexor XR, may increase the risk of bleeding events, ranging from ecchymoses, hematomas, epistaxis, petechiae, and gastrointestinal hemorrhage to life-threatening hemorrhage. Concomitant use of aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), warfarin, and other anti-coagulants or other drugs known to affect platelet function may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Caution patients about the risk of bleeding associated with the concomitant use of Effexor XR and NSAIDs, aspirin, or other drugs that affect coagulation.

5.5 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including Effexor XR may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.6 Activation of Mania/Hypomania

Mania or hypomania was reported in Effexor XR treated patients in the premarketing studies in MDD, SAD, and PD (see Table 2). Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs to treat MDD. Effexor XR should be used cautiously in patients with a history of mania or hypomania.

Table 2: Incidence (%) of Mania or Hypomania Reported in Effexor XR Treated Patients in the Premarketing Studies

Indication	Effexor XR	Placebo
MDD	0.3	0.0
GAD	0.0	0.2
SAD	0.2	0.0
PD	0.1	0.0

5.7 Discontinuation Syndrome

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, including prospective analyses of clinical studies in GAD and retrospective surveys of studies in MDD and SAD. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated

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with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, flu-like symptoms, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor XR, other SNRIs, and SSRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor XR. A gradual reduction in the dose, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [*see Dosage and Administration (2.8)*].

5.8 Seizures

Seizures have occurred with venlafaxine therapy. Effexor XR, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures. [Must mitigate the risk: Risk factors, concomitant meds that lower the seizure threshold.]

5.9 Hyponatremia

Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Effexor XR. In many cases, the hyponatremia appears to be the result of the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs [*see Use in Specific Populations (8.5)*]. Also, patients taking diuretics, or those who are otherwise volume-depleted, may be at greater risk. Consider discontinuation of Effexor XR in patients with symptomatic hyponatremia, and institute appropriate medical intervention.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.10 Weight and Height Changes in Pediatric Patients

Weight Changes

The average change in body weight and incidence of weight loss (percentage of patients who lost 3.5% or more) in the placebo-controlled pediatric studies in MDD, GAD, and SAD are shown in Tables 3 and 4.

Table 3: Average Change in Body Weight (kg) From Beginning of Treatment in Pediatric Patients in Double-blind, Placebo-controlled Studies of Effexor XR

Indication (Duration)	Effexor XR	Placebo
MDD and GAD	-0.45 (n = 333)	+0.77 (n = 333)

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Table 3: Average Change in Body Weight (kg) From Beginning of Treatment in Pediatric Patients in Double-blind, Placebo-controlled Studies of Effexor XR

Indication (Duration)	Effexor XR	Placebo
(4 pooled studies, 8 weeks)		
SAD (16 weeks)	-0.75 (n = 137)	+0.76 (n = 148)

Table 4: Incidence (%) of Pediatric Patients Experiencing Weight Loss (3.5% or more) in Double-blind, Placebo-controlled Studies of Effexor XR

Indication (Duration)	Effexor XR	Placebo
MDD and GAD (4 pooled studies, 8 weeks)	18[a] (n = 333)	3.6 (n = 333)
SAD (16 weeks)	47[a] (n = 137)	14 (n = 148)

[a] $p < 0.001$ versus placebo

Weight loss was not limited to patients with treatment-emergent anorexia [*see Warnings and Precautions (5.11)*].

The risks associated with longer term Effexor XR use were assessed in an open-label MDD study of children and adolescents who received Effexor XR for up to six months. The children and adolescents in the study had increases in weight that were less than expected, based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (< 12 years old) than for adolescents (≥ 12 years old).

Height Changes

Table 5 shows the average height increase in pediatric patients in the short-term, placebo-controlled MDD, GAD, and SAD studies. The differences in height increases in GAD and MDD studies were most notable in patients younger than twelve.

Table 5: Average Height Increases (cm) in Pediatric Patients in Placebo-controlled Studies of Effexor XR

Indication (Duration)	Effexor XR	Placebo
MDD (8 weeks)	0.8 (n = 146)	0.7 (n = 147)
GAD (8 weeks)	0.3[a] (n = 122)	1.0 (n = 132)
SAD (16 weeks)	1.0 (n = 109)	1.0 (n = 112)

[a] $p = 0.041$

In the six-month, open-label MDD study, children and adolescents had height increases that were less than expected, based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children (< 12 years old) than for adolescents (≥ 12 years old).

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5.11 Appetite Changes in Pediatric Patients

Decreased appetite (reported as treatment-emergent anorexia) was more commonly observed in Effexor XR treated patients versus placebo-treated patients in the premarketing evaluation of Effexor XR for MDD, GAD, and SAD (see Table 6).

Table 6: Incidence (%) of Decreased Appetite and Associated Discontinuation Rates[a] (%) in Pediatric Patients in Placebo-controlled Studies of Effexor XR

Indication (Duration)	Effexor XR Incidence	Discontinuation	Placebo Incidence	Discontinuation
MDD and GAD (pooled, 8 weeks)	10	0.0	3	–
SAD (16 weeks)	22	0.7	3	0.0

[a] The discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo.

5.12 Interstitial Lung Disease and Eosinophilic Pneumonia

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse events should be considered in venlafaxine-treated patients who present with progressive dyspnea, cough or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hypersensitivity [*see Contraindications (4.1)*]
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Adults [*see Warnings and Precautions (5.1)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.2)*]
- Elevations in Blood Pressure [*see Warnings and Precautions (5.3)*]
- Abnormal Bleeding [*see Warnings and Precautions (5.4)*]
- Angle Closure Glaucoma [*see Warnings and Precautions (5.5)*]
- Activation of Mania/Hypomania [*see Warnings and Precautions (5.6)*]
- Discontinuation Syndrome [*see Warnings and Precautions (5.7)*]
- Renal Impairment [*see Warnings and Precautions (2.6)*]
- Hepatic Impairment [*see Warnings and Precautions (2.6)*]
- Seizure [*see Warnings and Precautions (5.8)*]
- Hyponatremia [*see Warnings and Precautions (5.9)*]
- Weight and Height changes in Pediatric Patients [*see Warnings and Precautions (5.10)*]
- Appetite Changes in Pediatric Patients [*see Warnings and Precautions (5.11)*]
- Interstitial Lung Disease and Eosinophilic Pneumonia [*see Warnings and Precautions (5.12)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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Most Common Adverse Reactions

The most commonly observed adverse reactions in the clinical study database in Effexor XR treated patients in MDD, GAD, SAD, and PD (incidence ≥ 5% and at least twice the rate of placebo) were: nausea (30.0%), somnolence (15.3%), dry mouth (14.8%), sweating (11.4%), abnormal ejaculation (9.9%), anorexia (9.8%), constipation (9.3%), impotence (5.3%) and decreased libido (5.1%).

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

Combined across short-term, placebo-controlled premarketing studies for all indications, 12% of the 3,558 patients who received Effexor XR (37.5-225 mg) discontinued treatment due to an adverse experience, compared with 4% of the 2,197 placebo-treated patients in those studies.

The most common adverse reactions leading to discontinuation in ≥ 1% of the Effexor XR treated patients in the short-term studies (up to 12 weeks) across indications are shown in Table 7.

Table 7: Incidence (%) of Patients Reporting Adverse Reactions Leading to Discontinuation in Placebo-controlled Clinical Studies (up to 12 Weeks Duration)

Body System **Adverse Reaction**	**Effexor XR** **n = 3,558**	**Placebo** **n = 2,197**
Body as a whole		
Asthenia	1.7	0.5
Headache	1.5	0.8
Digestive system		
Nausea	4.3	0.4
Nervous system		
Dizziness	2.2	0.8
Insomnia	2.1	0.6
Somnolence	1.7	0.3
Skin and appendages	1.5	0.6
Sweating	1.0	0.2

Common Adverse Reactions in Placebo-controlled Studies

The number of patients receiving multiple doses of Effexor XR during the premarketing assessment for each approved indication is shown in Table 8. The conditions and duration of exposure to venlafaxine in all development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies.

Table 8: Patients Receiving Effexor XR in Premarketing Clinical Studies

Indication	**Effexor XR**
MDD	705[a]
GAD	1,381
SAD	819
PD	1,314

[a] In addition, in the premarketing assessment of Effexor, multiple doses were administered to 2,897 patients in studies for MDD.

The incidences of common adverse reactions (those that occurred in ≥ 2% of Effexor XR treated patients [357 MDD patients, 1,381 GAD patients, 819 SAD patients, and 1,001 PD patients] and more frequently

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than placebo) in Effexor XR treated patients in short-term, placebo-controlled, fixed- and flexible-dose clinical studies (doses 37.5 to 225 mg per day) are shown in Table 9.

The adverse reaction profile did not differ substantially between the different patient populations.

Table 9: Common Adverse Reactions: Percentage of Patients Reporting Adverse Reactions (≥ 2% and > placebo) in Placebo-controlled Studies (up to 12 Weeks Duration) across All Indications

Body System **Adverse Reaction**	**Effexor XR** **n = 3,558**	**Placebo** **n = 2,197**
Body as a whole		
Asthenia	12.6	7.8
Cardiovascular system		
Hypertension	3.4	2.6
Palpitation	2.2	2.0
Vasodilatation	3.7	1.9
Digestive system		
Anorexia	9.8	2.6
Constipation	9.3	3.4
Diarrhea	7.7	7.2
Dry mouth	14.8	5.3
Nausea	30.0	11.8
Vomiting	4.3	2.7
Nervous system		
Abnormal dreams	2.9	1.4
Dizziness	15.8	9.5
Insomnia	17.8	9.5
Libido decreased	5.1	1.6
Nervousness	7.1	5.0
Paresthesia	2.4	1.4
Somnolence	15.3	7.5
Tremor	4.7	1.6
Respiratory system		
Yawn	3.7	0.2
Skin and appendages		
Sweating (including night sweats)	11.4	2.9
Special senses		
Abnormal vision	4.2	1.6
Urogenital system		
Abnormal ejaculation/orgasm (men)[a]	9.9	0.5
Anorgasmia (men)[a]	3.6	0.1
Anorgasmia (women)[b]	2.0	0.2
Impotence (men)[a]	5.3	1.0

[a] Percentages based on the number of men (Effexor XR, n = 1,440; placebo, n = 923)
[b] Percentages based on the number of women (Effexor XR, n = 2,118; placebo, n = 1,274)

Other Adverse Reactions Observed in Clinical Studies

Body as a whole – Photosensitivity reaction
Cardiovascular system – Postural hypotension, syncope, hypotension, tachycardia
Digestive system – Gastrointestinal hemorrhage [*see Warnings and Precautions (5.4)*], bruxism

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Hemic/Lymphatic system – Ecchymosis [*see Warnings and Precautions (5.4)*]
Metabolic/Nutritional – Hypercholesterolemia, weight gain [*see Warnings and Precautions (5.10)*], weight loss [*see Warnings and Precautions (5.10)*]
Nervous system – Seizures [*see Warnings and Precautions (5.8)*], manic reaction [*see Warnings and Precautions (5.6)*], agitation, confusion, akathisia, hallucinations, hypertonia, myoclonus, depersonalization, apathy
Skin and appendages – Urticaria, pruritus, rash, alopecia
Special senses – Mydriasis, abnormality of accommodation, tinnitus, taste perversion
Urogenital system – Urinary retention, urination impaired, urinary incontinence, urinary frequency increased, menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia)

6.2 Vital Sign Changes

In placebo-controlled premarketing studies, there were increases in mean blood pressure (see Table 10). Across most indications, a dose-related increase in mean supine systolic and diastolic blood pressure was evident in patients treated with Effexor XRs. Across all clinical studies in MDD, GAD, SAD and PD, 1.4% of patients in the Effexor XR groups experienced an increase in SDBP of ≥15 mm Hg along with a blood pressure ≥ 105 mm Hg, compared to 0.9% of patients in the placebo groups. Similarly, 1% of patients in the Effexor XR groups experienced an increase in SSBP of ≥ 20 mm Hg with a blood pressure ≥ 180 mm Hg, compared to 0.3% of patients in the placebo groups.

Table 10: Final On-therapy Mean Changes From Baseline in Supine Systolic (SSBP) and Diastolic (SDBP) Blood Pressure (mm Hg) in Placebo-controlled Studies

	Effexor XR				**Placebo**	
Indication	**≤ 75 mg per day**		**> 75 mg per day**			
(Duration)	**SSBP**	**SDBP**	**SSBP**	**SDBP**	**SSBP**	**SDBP**
MDD						
(8-12 weeks)	-0.28	0.37	2.93	3.56	-1.08	-0.10
GAD						
(8 weeks)	-0.28	0.02	2.40	1.68	-1.26	-0.92
(6 months)	1.27	-0.69	2.06	1.28	-1.29	-0.74
SAD						
(12 weeks)	-0.29	-1.26	1.18	1.34	-1.96	-1.22
(6 months)	-0.98	-0.49	2.51	1.96	-1.84	-0.65
PD						
(10-12 weeks)	-1.15	0.97	-0.36	0.16	-1.29	-0.99

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Effexor XR treatment was associated with sustained hypertension (defined as treatment-emergent Supine Diastolic Blood Pressure [SDBP] ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for three consecutive on-therapy visits (see Table 11). An insufficient number of patients received mean doses of Effexor XR over 300 mg per day in clinical studies to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

Table 11: Sustained Elevations in SDBP in Effexor XR Premarketing Studies

Indication	Dose Range (mg per day)	Incidence (%)
MDD	75-375	19/705 (3)
GAD	37.5-225	5/1011 (0.5)
SAD	75-225	5/771 (0.6)
PD	75-225	9/973 (0.9)

Effexor XR was associated with mean increases in pulse rate compared with placebo in premarketing placebo-controlled studies (see Table 12) [*see Warnings and Precautions (5.3, 5.4)*].

Table 12: Approximate Mean Final On-therapy Increase in Pulse Rate (beats/min) in Effexor XR Premarketing Placebo-controlled Studies (up to 12 Weeks Duration)

Indication (Duration)	Effexor XR	Placebo
MDD (12 weeks)	2	1
GAD (8 weeks)	2	< 1
SAD (12 weeks)	3	1
PD (12 weeks)	1	< 1

6.3 Laboratory Changes

Serum Cholesterol

Effexor XR was associated with mean final increases in serum cholesterol concentrations compared with mean final decreases for placebo in premarketing MDD, GAD, SAD and PD clinical studies (Table 13).

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Table 13: Mean Final On-therapy Changes in Cholesterol Concentrations (mg/dL) in Effexor XR Premarketing Studies

Indication (Duration)	Effexor XR	Placebo
MDD		
(12 weeks)	+1.5	-7.4
GAD		
(8 weeks)	+1.0	-4.9
(6 months)	+2.3	-7.7
SAD		
(12 weeks)	+7.9	-2.9
(6 months)	+5.6	-4.2
PD		
(12 weeks)	5.8	-3.7

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. 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 while placebo subjects experienced mean final decreases of 4.9 mg/dL and 7.7 mg/dL, respectively. Effexor XR treatment for up to 12 weeks and up to 6 months in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 7.9 mg/dL and 5.6 mg/dL, respectively, compared with mean final decreases of 2.9 and 4.2 mg/dL, respectively, for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 5.8 mg/dL compared with a mean final decrease of 3.7 mg/dL for placebo.

Patients treated with Effexor (immediate release) 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 compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients.

Serum Triglycerides

Effexor XR was associated with mean final on-therapy increases in fasting serum triglycerides compared with placebo in premarketing clinical studies of SAD and PD up to 12 weeks (pooled data) and 6 months duration (Table 14).

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Table 14: Mean Final On-therapy Increases in Triglyceride Concentrations (mg/dL) in Effexor XR Premarketing Studies

Indication (Duration)	Effexor XR	Placebo
SAD (12 weeks)	8.2	0.4
SAD (6 months)	11.8	1.8
PD (12 weeks)	5.9	0.9
PD (6 months)	9.3	0.3

6.4 Pediatric Patients

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical studies) 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 Warnings and Precautions (5.3, 5.10, 5.11) and Use in Specific Populations (8.4)*].

In pediatric clinical studies, the adverse reaction, suicidal ideation, was observed.

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

6.5 Adverse Reactions Identified During Postapproval Use

The following adverse reactions have been identified during postapproval use of Effexor XR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Body as a whole – Anaphylaxis, angioedema
Cardiovascular system – QT prolongation, ventricular fibrillation, ventricular tachycardia (including torsade de pointes)
Digestive system – Pancreatitis
Hemic/Lymphatic system – Mucous membrane bleeding [*see Warnings and Precautions (5.4)*], blood dyscrasias (including agranulocytosis, aplastic anemia, neutropenia and pancytopenia), prolonged bleeding time, thrombocytopenia
Metabolic/Nutritional – Hyponatremia [*see Warnings and Precautions (5.9)*], Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion [*see Warnings and Precautions (5.9)*], abnormal liver function tests, hepatitis, prolactin increased
Musculoskeletal – Rhabdomyolysis
Nervous system – Neuroleptic Malignant Syndrome (NMS) [*see Warnings and Precautions (5.2)*], serotonergic syndrome [*see Warnings and Precautions (5.2)*], delirium, extrapyramidal reactions (including dystonia and dyskinesia), impaired coordination and balance, tardive dyskinesia
Respiratory system – Pulmonary eosinophilia
Skin and appendages – Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Special senses – Angle-closure glaucoma [*see Warnings and Precautions (5.5)*]

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7 DRUG INTERACTIONS

7.1 Central Nervous System (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 Effexor XR is taken in combination with other CNS-active drugs.

7.2 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 antidepressants with pharmacological properties similar to Effexor XR (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Dosage and Administration (2.9), Contraindications (4.2) and Warnings and Precautions (5.2)*].

7.3 Serotonergic Drugs

Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's wort. If concomitant treatment with Effexor XR and these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended [*see Dosage and Administration (2.9), Contraindications (4.2), and Warnings and Precautions (5.2)*].

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. The use of psychotropic drugs that interfere with serotonin reuptake is associated with the occurrence of upper gastrointestinal bleeding and concurrent use of an NSAID or aspirin may potentiate this risk of bleeding [*see Warnings and Precautions (5.4)*]. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Effexor XR is initiated or discontinued.

7.5 Weight Loss Agents

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products.

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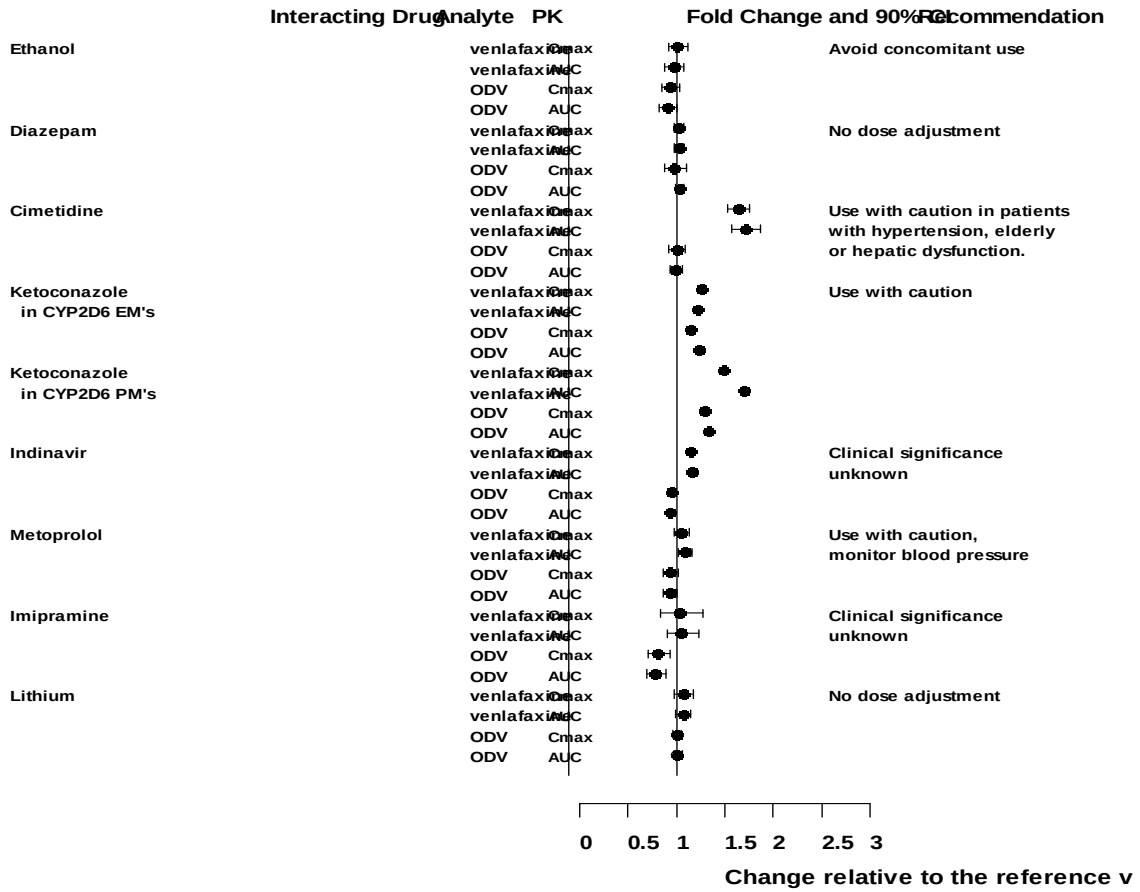
7.6 Effects of Other Drugs on Effexor XR

Figure 1: Effect of interacting drugs on the pharmacokinetics of venlafaxine and active metabolite O-desmethylvenlafaxine (ODV).



Abbreviations: ODV, O-desmethylvenlafaxine; AUC, area under the curve; Cmax, peak plasma concentrations; EM's, extensive metabolizers; PM's, poor metabolizers

* No dose adjustment on co-administration with CYP2D6 inhibitors (Fig 3 and Metabolism Section 12.3)

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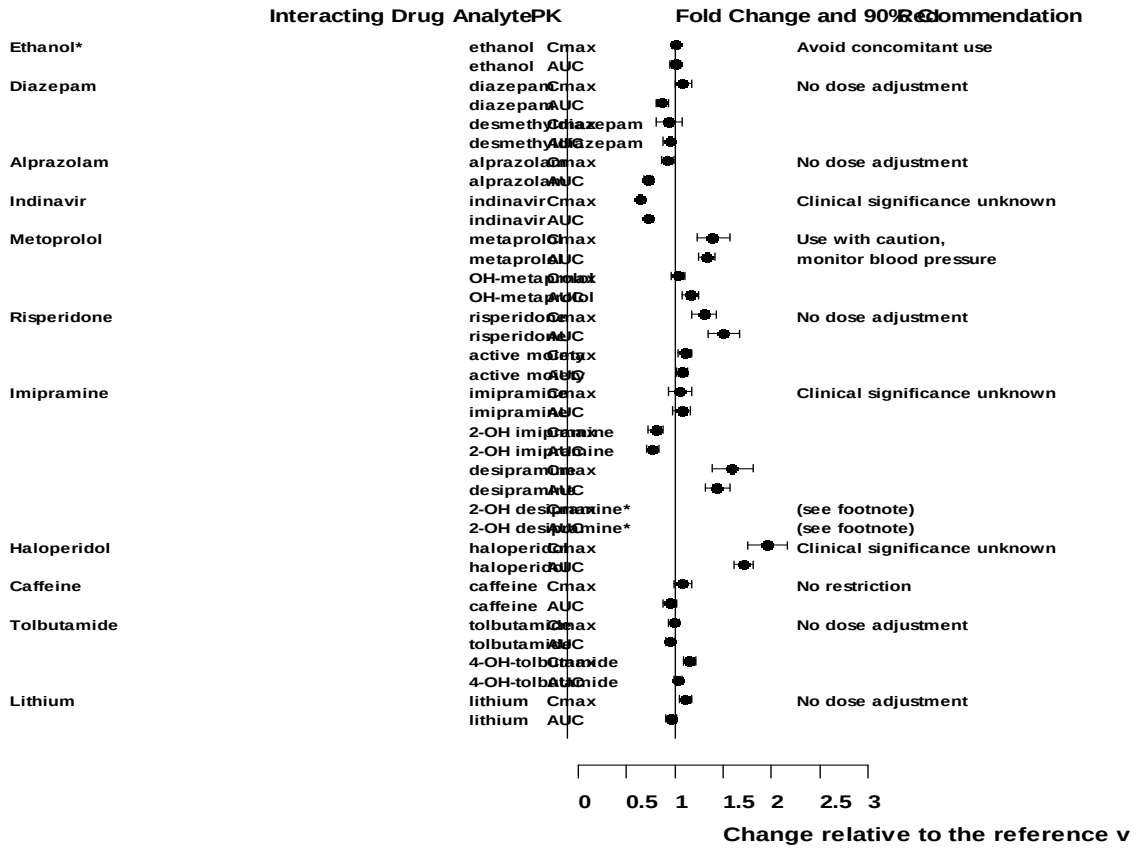
7.7 Effects of Effexor XR on Other Drugs

Figure 2: Effect of venlafaxine on the pharmacokinetics interacting drugs and their active metabolites.



Abbreviations: AUC, area under the curve; Cmax, peak plasma concentrations; OH, hydroxyl

* Data for 2-OH desipramine were not plotted to enhance clarity; the fold change and 90% CI for Cmax and AUC of 2-OH desipramine were 6.6 (5.5, 7.9) and 4.4 (3.8, 5.0), respectively.

Note:
*: Administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

7.8 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects – Pregnancy Category C

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there

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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 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. In reproductive developmental studies in rats and rabbits with O-desmethylvenlafaxine (ODV), the major human metabolite of venlafaxine, evidence of teratogenicity was not observed at exposure margins of 13 in rats and 0.3 in rabbits. There are no adequate and well-controlled studies in pregnant women. Effexor XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Neonates exposed to Effexor XR, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs, or possibly a drug discontinuation syndrome. It should be noted, that in some cases the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*]. When treating a pregnant woman with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

8.2 Labor and Delivery

The effect of venlafaxine on labor and delivery in humans is unknown.

8.3 Nursing Mothers

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.

8.4 Pediatric Use

Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of Effexor XR in a child or adolescent must balance the potential risks with the clinical need [*see Boxed Warning, Warnings and Precautions (5.1, 5.10, 5.11) and Adverse Reactions (6.4)*].

Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height *(see Warnings and Precautions (5.10)).* Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if treatment is to be continued long-term [*see Warnings and Precautions (5.10, 5.11)*]. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six months in duration. In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to

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be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients [*see Warnings and Precautions (5.3,6.3)*].

8.5 Geriatric Use

The percentage of patients in clinical studies for Effexor XR for MDD, GAD, SAD, and PD who were 65 years of age or older are shown in Table 15.

Table 15: Percentage (and Number of Patients Studied) of Patients 65 Years of Age and Older by Indication[a]

Indication	Effexor XR
MDD	4 (14/357)
GAD	6 (77/1,381)
SAD	1 (10/819)
PD	2 (16/1,001)

[a] In addition, in the premarketing assessment of Effexor (immediate release), 12% (357/2,897) of patients were ≥ 65 years of age.

No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Effexor XR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.9)*].

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly [*see Clinical Pharmacology (12.3) and* (see Figure 3)]. No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction [*see Dosage and Administration (2.6)*].

8.6 Age and Gender

A population pharmacokinetic analysis of 404 Effexor-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary [*see Dosage and Administration (2.6)*] (see Table 15).

8.7 Use in Patient Subgroups

Figure 3: Pharmacokinetics of venlafaxine and its metabolite O-desmethylvenlafaxine (ODV) in special populations.

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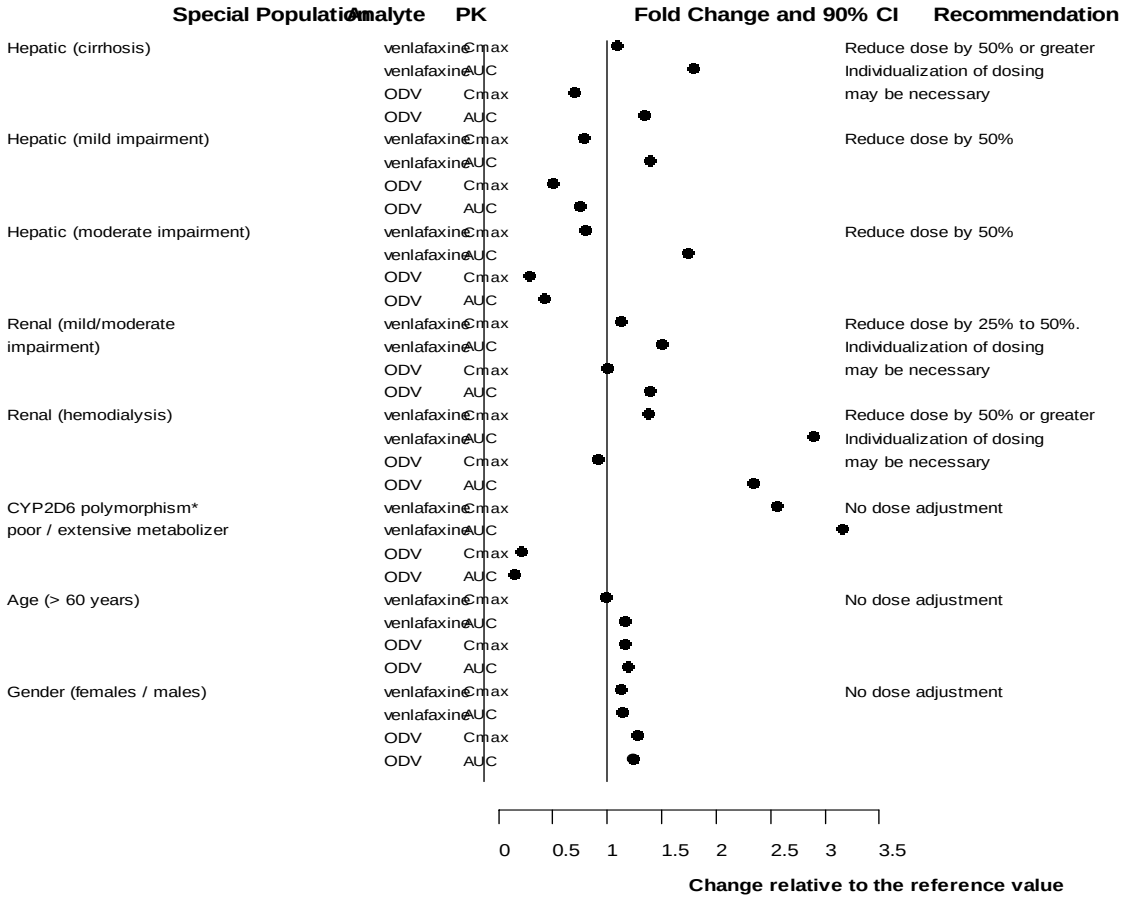

Abbreviations: ODV, O-desmethylvenlafaxine; AUC, area under the curve; Cmax, peak plasma concentrations;
*Similar effect is expected with strong CYP2D6 inhibitors

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Effexor XR is not a controlled substance.

9.2 Abuse

While venlafaxine has not been systematically studied in clinical studies for its potential for abuse, there was no indication of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

9.3 Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors.

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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. Discontinuation effects have been reported in patients receiving venlafaxine [*see Dosage and Administration (2.8)*].

10 OVERDOSAGE

10.1 Human Experience

During the premarketing evaluations of Effexor XR (for MDD, GAD, SAD, and PD) and Effexor (for MDD), there were twenty reports of acute overdosage with Effexor (6 and 14 reports in Effexor XR and Effexor patients, respectively), either alone or in combination with other drugs and/or alcohol.

Somnolence was the most commonly reported symptom. Among the other reported symptoms were paresthesia of all four limbs, moderate dizziness, nausea, numb hands and feet, and hot-cold spells 5 days after the overdose. In most cases, no signs or symptoms were associated with overdose. The majority of the reports involved ingestion in which the total dose of venlafaxine taken was estimated to be no more than several-fold higher than the usual therapeutic dose. One patient who ingested 2.75 g of venlafaxine was observed to have two generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in two of the other patients.

Actions taken to treat the overdose included no treatment, hospitalization and symptomatic treatment, and hospitalization plus treatment with activated charcoal. All patients recovered.

In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

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 preexisting burden of suicide risk factors than SSRI-treated 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 characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice (1-800-222-1222 or www.poison.org). In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Provide supportive and symptomatic measures.

11 DESCRIPTION

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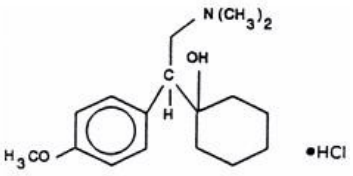
Effexor XR is an extended-release capsule for once-a-day oral administration that contains venlafaxine hydrochloride, a serotonin and norepinephrine reuptake inhibitor (SNRI).
Venlafaxine is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.86. The structural formula is shown as follows:



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid, with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.
Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH-dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of the antidepressant action of venlafaxine in humans is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake. Non- clinical studies have demonstrated that venlafaxine and its active metabolite, ODV, are potent and selective inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

12.2 Pharmacodynamics

Venlafaxine and ODV have no significant affinity for muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

12.3 Pharmacokinetics

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg per day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

Absorption and Distribution

Venlafaxine is well absorbed and extensively metabolized in the liver. ODV is the major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is approximately 45%.

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Administration of Effexor XR (150 mg once daily) generally resulted in lower C_{max} and later T_{max} values than for Effexor (immediate release) administered twice daily (Table 16). When equal daily doses of venlafaxine were administered as either an immediate-release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Therefore, Effexor XR provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet.

Table 16: Comparison of C_{max} and T_{max} Values for Venlafaxine and ODV Following Oral Administration of Effexor **XR and Effexor (Immediate Release)**

	Venlafaxine		**ODV**	
	C_{max} (ng/mL)	**T_{max} (h)**	**C_{max} (ng/mL)**	**T_{max} (h)**
Effexor XR (150 mg once daily)	150	5.5	260	9
Effexor (75 mg twice daily)	225	2	290	3

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM versus PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Effexor XR capsule.

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor XR to a patient taking another drug that is highly protein-bound should not cause increased free concentrations of the other drug.

Metabolism and Elimination

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (poor metabolizers) had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 levels (extensive metabolizers) [*see Use in Specific Populations 8.7*].

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Tumors were not increased by venlafaxine treatment in mice or rats. 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 the O-desmethyl metabolite (ODV) were lower in rats than in patients receiving the maximum recommended dose. O-desmethylvenlafaxine (ODV), the major human metabolite of venlafaxine, administered by oral gavage to

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mice and rats for 2 years did not increase the incidence of tumors in either study. Mice received ODV at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The exposure at the 300 mg/kg/day dose is 9 times that of a human dose of 225 mg/day. Rats received ODV at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The exposure at the highest dose is approximately 8 (males) or 11 (females) times that of a human dose of 225 mg/day.

Mutagenesis

Venlafaxine and the major human metabolite, 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 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. ODV was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay or in the *in vivo* chromosomal aberration assay in rats.

Impairment of Fertility

Reproduction and fertility studies of venlafaxine in rats showed no adverse effects of venlafaxine on male or female fertility at oral doses of up to 2 times the maximum recommended human dose of 225 mg/day on a mg/m^2 basis. However, reduced fertility was observed in a study in which male and female rats were treated with O-desmethylvenlafaxine (ODV), the major human metabolite of venlafaxine, prior to and during mating and gestation. This occurred at an ODV exposure (AUC) approximately 2 to 3 times that associated with a human venlafaxine dose of 225 mg/day.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

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

A 4-week study of inpatients meeting DSM-III-R criteria for MDD with melancholia utilizing Effexor in a range of 150 to 375 mg per day (divided in a three-times-a-day schedule) demonstrated superiority of Effexor over placebo based on the HAM-D-21 total score. The mean dose in completers was 350 mg per day (study 3).

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

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Patients receiving continued Effexor XR treatment experienced statistically significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo (study 4).

In a second longer term trial, adult outpatients with MDD, recurrent type, who had responded (HAM-D-21 total score ≤ 12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAM-D-21 total score ≥ 20; (2) no more than 2 HAM-D-21 total scores > 10, and (3) no single CGI Severity of Illness item score ≥ 4 (moderately ill)] during an initial 26 weeks of treatment on Effexor [100 to 200 mg per day, on a twice daily schedule] were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity of Illness item score ≥ 4, was for up to 52 weeks. Patients receiving continued Effexor treatment experienced statistically significantly lower relapse rates over the subsequent 52 weeks compared with those receiving placebo (study 5).

Table 17: Major Depressive Disorder Studies:

Study number	**Treatment Group**		**Primary Efficacy Measure: HAM-D Score**	
		MeanBaseline Score (SD)	**LSMean Changefrom Baseline**	**Placebo SubtractedDifferencea (95%CI)**
Study 1	Effexor(XR 75-225 mg/day)*	24.5	-11.7	-4.45(-6.66,-2.25)
	Placebo	23.6	-7.24	-
Study 2	Effexor(XR 75-225 mg/day)*	24.5	-15.11	-6.40(-8.45,-4.34)
	Placebo	24.9	-8.71	
Study 3	Effexor(IR 150-375 mg/day)*	28.2 (0.5)	-14.9	-10.2 (-14.4,-6.0)
	Placebo	28.6 (0.6)	-4.7	-

SD: standard deviation; LS Mean: least-squares mean; CI: confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline
* Doses statistically significantly superior to placebo.

14.2 Generalized Anxiety Disorder

The efficacy of Effexor XR as a treatment for Generalized Anxiety Disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies (75 to 225 mg per day), one 6-month, placebo-controlled, flexible-dose study (75 to 225 mg per day), and one 6-month, placebo-controlled, fixed-dose study (37.5, 75, and 150 mg per day) in adult outpatients meeting DSM-IV criteria for GAD.

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

Two 6-month studies, one evaluating Effexor XR doses of 37.5, 75, and 150 mg per day (study 3) and the other evaluating Effexor XR doses of 75 to 225 mg per day (study 4), showed that daily doses of 75 mg

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or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale during 6 months of treatment. While there was also evidence for superiority over placebo for the 37.5 mg per day dose, this dose was not as consistently effective as the higher doses.

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

Table 18: Generalized Anxiety Disorder Studies:

Study Number	Treatment Group	Primary Efficacy Measure: HAM-A Score		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo Subtracted Difference[a] (95% CI)**
Study 1	Ven XR 75 mg	24.7	-11.1 (0.95)	-1.5 (-3.8, 0.8)
	Ven XR 150 mg	24.5	-11.7 (0.87)	-2.2 (-4.5, 0.1)
	Eff XR 225 mg	23.6	-12,1 (0.81)	-2.6 (-4.9, -0.3)
	Placebo	24.1	-9.5 (0.85)	
Study 2	Ven XR 75 mg	23.7	-10.6 (0.82)	-2.6 (-4.6, -0.5)
	Ven XR 150 mg	23.0	-9.8 (0.86)	-1.7 (-3.8, 0.3)
	Placebo	23.7	-8.0 (0.73)	
Study 3	Ven XR 37.5 mg	26.6 (0.4)	-13.8	-2.8 (-5.1, -0.6)
	Ven XR 75 mg	26.3 (0.4)	-15.5	-4.6 (-6.9, -2.3)
	Ven XR150 mg	26.3 (0.4)	-16.4	-5.5 (-7.8, -3.1)
	Placebo	26.7 (0.5)	-11.0	
Study 4	Ven XR 75-225 mg	25.0	-13.4 (0.79)	- 4.7 (-6.6, -2.9)
	Placebo	24.9	-8.7 (0.70)	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline
* Doses statistically significantly superior to placebo.

14.3 Social Anxiety Disorder (also known as Social Phobia)

The efficacy of Effexor XR as a treatment for Social Anxiety Disorder (SAD) was established in four double-blind, parallel-group, 12-week, multicenter, placebo-controlled, flexible-dose studies (studies 1-4) and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study, which included doses in a range of 75 to 225 mg per day in adult outpatients meeting DSM-IV criteria for SAD (study 5).

In these five studies, Effexor XR was statistically significantly more effective than placebo on change from baseline to endpoint on the Liebowitz Social Anxiety Scale (LSAS) total score. There was no evidence for any greater effectiveness of the 150 to 225 mg per day group compared to the 75 mg per day group in the 6-month study.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

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Table 19: Social Anxiety Disorder Studies

Study Number	Treatment Group	Primary Efficacy Measure: LSAS Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo Subtracted Difference[a] (95% CI)
Study 1	Ven XR (75-225 mg)	91.1	-31.0(2.22)	11.2 (-5.3, -17.1)
	Placebo	86.7	-19.9 (2.22)	-
Study 2	Ven XR (75-225 MG)	90.8	-32.8 (2.69)	-10.7 (-3.7,-17.6)
	Placebo	87.4	-22.1 (2.66)	-
Study 3	Ven XR (75-225 MG)	83.2	-36.0 (2.35)	-16.9(-22.6, -11.2)
	Placebo	83.6	-19.1 (2.40)	-12.7 (-6.5, -19.0)
Study 4	Ven XR (75-225 mg)	86.2	-35.0 (2.64)	-14.6 (-21.8, -7.4)
	Placebo	86.1	-22.2 (2,47)	
Study 5	Ven XR 75 mg	91.8	-38.1 (3.16)	-14.6 (-21.8, -7.4)
	Ven XR (150-225 mg)	86.2	-37.6 (3.05)	-14.1 (-21.3, -6.9)
	Placebo	89.3	-23.5 (3.08)	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline
* Doses statistically significantly superior to placebo.

14.4 Panic Disorder

The efficacy of Effexor XR as a treatment for Panic Disorder (PD) was established in two double-blind, 12-week, multicenter, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for PD, with or without agoraphobia. Patients received fixed doses of 75 or 150 mg per day in one study (study 1) and 75 or 225 mg per day in the other study (study 2).

Efficacy was assessed on the basis of outcomes in three variables: (1) percentage of patients free of full-symptom panic attacks on the Panic and Anticipatory Anxiety Scale (PAAS); (2) mean change from baseline to endpoint on the Panic Disorder Severity Scale (PDSS) total score; and (3) percentage of patients rated as responders (much improved or very much improved) on the Clinical Global Impressions (CGI) Improvement scale. In these two studies, Effexor XR was statistically significantly more effective than placebo (for each fixed dose) on all three endpoints, but a dose-response relationship was not clearly established.

Examination of subsets of the population studied did not reveal any differential responsiveness on the basis of gender. There was insufficient information to determine the effect of age or race on outcome in these studies.

In a longer term study (study 3), adult outpatients meeting DSM-IV criteria for PD who had responded during a 12-week open phase with Effexor XR (75 to 225 mg per day) were randomly assigned to continue the same Effexor XR dose (75, 150, or 225 mg) or switch to placebo for observation for relapse under double-blind conditions. Response during the open phase was defined as ≤ 1 full-symptom panic attack per week during the last 2 weeks of the open phase and a CGI Improvement score of 1 (very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks or having discontinued due to loss of effectiveness as determined by the investigators during the study. Randomized patients were in response status for a mean time of 34 days prior to being randomized. In the randomized phase following the 12-

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week open-label period, patients receiving continued Effexor XR experienced a statistically significantly longer time to relapse.

Table 20: Panic Disorder Studies:

Study Number	Treatment Group	Primary Efficacy Measure: Whether Free of Full-symptom Panic Attacks		
		Percent of patients Free of Full symptom panic attack	Adjusted Odds Ratio[a] to placebo	Adjusted Odds Ratio[a] 95% Confidence Interval
Study 1	Ven XR 75 mg* Ven XR 150 mg* Placebo	54.1% (85/157) 61.4% (97/158) 34.4% (53/154)	2. 268 3.035 --	(1.43, 3.59) (1.91, 4.82) --
Study 2	Ven XR 75 mg* Ven XR 225 mg* Placebo	64.1% (100/156) 70.0% (112/160) 46.5% (73/157)	2.350 2.890 --	(1.46, 3.78) (1.80, 4.64) --

[a] Odds ratio (drug to placebo) in terms of probability of free of full-symptom panic attacks based on logistic regression model.
95%CI: 95% confidence interval without adjusting for multiple dose arms.
* Doses statistically significantly superior to placebo.

14.5 Pediatric Patients

Two placebo-controlled studies in 766 pediatric patients with MDD and two placebo-controlled studies in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Effexor XR® (venlafaxine hydrochloride) extended-release capsules are available as follows:

- 37.5 mg, grey cap/peach body with “W” and “Effexor XR” on the cap and “37.5” on the body.
  NDC 0008-0837-20, bottle of 15 capsules in unit-of-use package.
  NDC 0008-0837-21, bottle of 30 capsules in unit-of-use package.
  NDC 0008-0837-22, bottle of 90 capsules in unit-of-use package.
  NDC 0008-0837-03, carton of 10 Redipak® blister strips of 10 capsules each.
- 75 mg, peach cap and body with “W” and “Effexor XR” on the cap and “75” on the body.
  NDC 0008-0833-20, bottle of 15 capsules in unit-of-use package.
  NDC 0008-0833-21, bottle of 30 capsules in unit-of-use package.
  NDC 0008-0833-22, bottle of 90 capsules in unit-of-use package.
  NDC 0008-0833-03, carton of 10 Redipak® blister strips of 10 capsules each.
- 150 mg, dark orange cap and body with “W” and “Effexor XR” on the cap and “150” on the body.
  NDC 0008-0836-20, bottle of 15 capsules in unit-of-use package.
  NDC 0008-0836-21, bottle of 30 capsules in unit-of-use package.
  NDC 0008-0836-22, bottle of 90 capsules in unit-of-use package.
  NDC 0008-0836-03, carton of 10 Redipak® blister strips of 10 capsules each.

Store at controlled room temperature, 20° to 25°C (68° to 77°F).
The unit-of-use package is intended to be dispensed as a unit.
The appearance of these capsules is a trademark of Wyeth Pharmaceuticals.

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17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for Effexor XR. The prescriber or healthcare professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.
Patients should be advised of the following issues and should be asked to alert their prescriber if these occur while taking Effexor XR.

Suicidal Thoughts and Behaviors

Advise patients, their families and caregivers to look for the emergence of suicidality, worsening of depression, and other psychiatric symptoms (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, psychomotor restlessness, hypomania, mania, other unusual changes in behavior), especially early during treatment and when the dose is adjusted up or down. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring [*see Boxed Warning and Warnings and Precautions (5.1)*].

Concomitant Medication

Advise patients taking Effexor XR not to use concomitantly other products containing venlafaxine or desvenlafaxine. Healthcare professionals should instruct patients not to take Effexor XR with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping Effexor XR before starting an MAOI [*see Contraindications (4.2)*].

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome, with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, with antipsychotics or other dopamine antagonists, or other serotonergic agents [s*ee Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

Elevated Blood Pressure

Advise patients that they should have regular monitoring of blood pressure when taking Effexor XR [*see Warnings and Precautions (5.3)*].

Abnormal Bleeding

Patients should be cautioned about the concomitant use of Effexor XR and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding [*see Warnings and Precautions (5.4)*].

Angle Closure Glaucoma

Patients should be advised that taking Effexor XR can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with

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iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.5)]*.

Activation of Mania/Hypomania

Advise patients, their families and caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.6)*].

Cardiovascular/Cerebrovascular Disease

Caution is advised in administering Effexor XR to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*].

Serum Cholesterol and Triglyceride Elevation

Advise patients that elevations in total cholesterol, LDL and triglycerides may occur and that measurement of serum lipids may be considered [*see Warnings and Precautions (6.3)*].

Discontinuation [Symptoms]

Advise patients not to stop taking Effexor XR without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping Effexor XR [*see Warnings and Precautions* (*5.7) and Adverse Reactions (6.1)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that Effexor XR therapy does not adversely affect their ability to engage in such activities.

Alcohol

Advise patients to avoid alcohol while taking Effexor XR [*see Drug Interactions (7.6)*].

Allergic Reactions

Advise patients to notify their physician if they develop allergic phenomena such as rash, hives, swelling, or difficulty breathing.

Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy [*see Use in Specific Populations (8.1)*].

Nursing

Advise patients to notify their physician if they are breast-feeding an infant [*see Use in Specific Populations (8.3)*].

Residual Spheroids

Effexor XR contains spheroids, which release the drug slowly into the digestive tract. The insoluble portion of these spheroids is eliminated, and patients may notice spheroids passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the spheroids.

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Medication Guide

EFFEXOR XR(e-fex-or)
(venlafaxine hydrochloride)
(Extended-Release Capsules)

Read the Medication Guide that comes with **EFFEXOR XR** before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about EFFEXOR XR?

EFFEXOR XR and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **EFFEXOR XR and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults **within the first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
  - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
  - Pay particular attention to such changes when **EFFEXOR XR** is started or when the dose is changed.

  Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

  Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:
    - attempts to commit suicide
    - acting on dangerous impulses
    - acting aggressive or violent
    - thoughts about suicide or dying
    - new or worse depression
    - new or worse anxiety or panic attacks
    - feeling agitated, restless, angry or irritable
    - trouble sleeping
    - an increase in activity or talking more than what is normal for you
    - other unusual changes in behavior or mood
    - **Visual problems**
      - eye pain
      - changes in vision
      - swelling or redness in or around the eye

    Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. EFFEXOR XR may be associated with these serious side effects:

2. Serotonin Syndrome
This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

3. Changes in blood pressure. EFFEXOR XR may:

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- increase your blood pressure. Control high blood pressure before starting treatment and monitor blood pressure regularly

4. Enlarged pupils (mydriasis).
5. Anxiety and insomnia.
6. Changes in appetite or weight.
7. Manic/hypomanic episodes:
- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

8. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:
- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

9. Seizures or convulsions.
10. Abnormal bleeding: **EFFEXOR XR** and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.
11. Elevated cholesterol.
12. Lung disease and pneumonia: **EFFEXOR XR** may cause rare lung problems. Symptoms include:
- worsening shortness of breath
- cough
- chest discomfort

13. Severe allergic reactions:
- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain.

Do not stop EFFEXOR XR without first talking to your healthcare provider. Stopping **EFFEXOR XR** too quickly or changing from another antidepressant too quickly may cause serious symptoms including:
- anxiety, irritability
- feeling tired, restless or problems sleeping
- headache, sweating, dizziness
- electric shock-like sensations, shaking, confusion, nightmares
- vomiting, nausea, diarrhea

What is EFFEXOR XR?

EFFEXOR XR is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider.
EFFEXOR XR is also used to treat:
- Generalized Anxiety Disorder (GAD)
- Social Anxiety Disorder (SAD)
- Panic Disorder (PD)

Talk to your healthcare provider if you do not think that your condition is getting better with **EFFEXOR XR** treatment.

Who should not take EFFEXOR XR?
Do not take **EFFEXOR XR** if you:
- are allergic to **EFFEXOR XR** or any of the ingredients in **EFFEXOR XR**. See the end of this Medication Guide for a complete list of ingredients in **EFFEXOR XR**.
- have uncontrolled angle-closure glaucoma
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - Do not take an MAOI within 7 days of stopping **EFFEXOR XR** unless directed to do so by your physician.
  - Do not start **EFFEXOR XR** if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

People who take EFFEXOR XR close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:
- high fever
- uncontrolled muscle spasms
- stiff muscles

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- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)

What should I tell my healthcare provider before taking EFFEXOR XR? Ask if you are not sure.

Before starting **EFFEXOR XR**, tell your healthcare provider if you:

- Are taking certain drugs such as:
  - Medicines used to treat migraine headaches such as:
    - triptans
  - Medicines used to treat mood, anxiety, psychotic or thought disorders, such as:
    - tricyclic antidepressants
    - lithium
    - SSRIs
    - SNRIs
    - antipsychotic drugs
  - Medicines used to treat pain such as:
    - tramadol
  - Medicines used to thin your blood such as:
    - warfarin
  - Medicines used to treat heartburn such as:
    - Cimetidine
  - Over-the-counter medicines or supplements such as:
    - Aspirin or other NSAIDs
    - Tryptophan
    - St. John's Wort
- have heart problems
- have diabetes
- have liver problems
- have kidney problems
- have thyroid problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have high blood pressure
- have high cholesterol
- have or had bleeding problems
- are pregnant or plan to become pregnant. It is not known if **EFFEXOR XR** will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy
- are breast-feeding or plan to breast-feed. Some **EFFEXOR XR** may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking **EFFEXOR XR**.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. **EFFEXOR XR** and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take **EFFEXOR XR** with your other medicines. Do not start or stop any medicine while taking **EFFEXOR XR** without talking to your healthcare provider first.

If you take **EFFEXOR XR**, you should not take any other medicines that contain (venlafaxine) including: venlafaxine HCl.

How should I take EFFEXOR XR?

- Take **EFFEXOR XR** exactly as prescribed. Your healthcare provider may need to change the dose of **EFFEXOR XR** until it is the right dose for you.
- **EFFEXOR XR** is to be taken with food.
- If you miss a dose of **EFFEXOR XR**, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of **EFFEXOR XR** at the same time.
- If you take too much **EFFEXOR XR**, call your healthcare provider or poison control center right away, or get emergency treatment.
- When switching from another antidepressant to **EFFEXOR XR** your doctor may want to lower the dose of the initial antidepressant first to avoid side effects

What should I avoid while taking EFFEXOR XR?

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EFFEXOR XR can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how **EFFEXOR XR** affects you. Do not drink alcohol while using **EFFEXOR XR**.

What are the possible side effects of EFFEXOR XR?
EFFEXOR XR may cause serious side effects, including:

- See "What is the most important information I should know about **EFFEXOR XR**?"
- Increased cholesterol- have your cholesterol checked regularly
- Newborns whose mothers take **EFFEXOR XR** in the third trimester may have problems right after birth including:
  - problems feeding and breathing
  - seizures
  - shaking, jitteriness or constant crying
- Angle-closure glaucoma

Common possible side effects in people who take **EFFEXOR XR** include**:**

- unusual dreams
- sexual problems
- loss of appetite, constipation, diarrhea, nausea or vomiting, or dry mouth
- feeling tired, fatigued or overly sleepy
- change in sleep habits, problems sleeping
- yawning
- tremor or shaking
- dizziness, blurred vision
- sweating
- feeling anxious, nervous or jittery
- headache
- increase in heart rate

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of **EFFEXOR XR**. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store EFFEXOR XR?

- Store **EFFEXOR XR** at room temperature between 68°F and 77°F (20°C to 25°C).
- Keep **EFFEXOR XR** in a dry place.

Keep EFFEXOR XR and all medicines out of the reach of children.

General information about EFFEXOR
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use **EFFEXOR XR** for a condition for which it was not prescribed. Do not give **EFFEXOR XR** to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about **EFFEXOR XR**. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about **EFFEXOR XR** that is written for healthcare professionals.

For more information about **EFFEXOR XR** call **1-800-934-5556** or go to www. **EFFEXOR XR**.com.

What are the ingredients in EFFEXOR XR?

Active ingredient: (venlafaxine)
Inactive ingredients:

- **Extended-Release Capsules**: cellulose, ethylcellulose, gelatin, hypromellose, iron oxides, and titanium dioxide.

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This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

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