

EFEXOR[®]-XR

Venlafaxine Hydrochloride

Modified Release Capsules

NAME OF THE MEDICINE

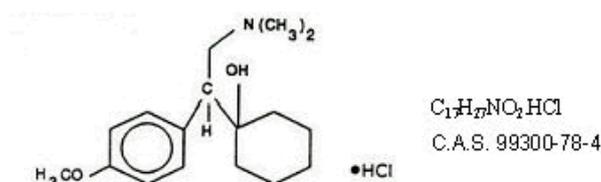
EFEXOR-XR

Venlafaxine hydrochloride 37.5 mg, 75 mg and 150 mg modified release capsules.

DESCRIPTION

EFEXOR-XR capsules are an extended-release formulation, which release the active constituent, venlafaxine hydrochloride, from spheroids within the capsule. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Three strengths of EFEXOR-XR capsules are available containing either 37.5 mg, 75 mg or 150 mg of venlafaxine (as hydrochloride).

Venlafaxine hydrochloride is chemically defined (R/S)-1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride. It 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 molecular weight is 313.87.



Other ingredients are cellulose-microcrystalline, ethylcellulose and hypromellose. The capsule shell contains gelatin, red iron oxide CI 77491, yellow iron oxide CI 77492, titanium dioxide and talc purified. In addition to these, the 37.5 mg capsule shells also contain black iron oxide CI 77499. The 37.5 mg and 75 mg capsule shells are branded with Opacode S-1-15094/S-1-15095 red ink. The 150 mg capsule shells are branded with TekPrint SB-0007P white ink.

PHARMACOLOGY

Actions

Venlafaxine is a structurally novel antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents.

The antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of serotonin and noradrenaline reuptake, and also weakly inhibit dopamine reuptake. Venlafaxine is a racemate. The R-enantiomer is relatively more potent than the S-enantiomer with regard to inhibition of noradrenaline reuptake; the S-enantiomer is more potent regarding inhibition of serotonin reuptake. Both enantiomers are more potent on serotonin compared to noradrenaline reuptake. The enantiomers of ODV also inhibit both noradrenaline and serotonin reuptake, with the R-enantiomer being more potent. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake and receptor binding. Studies in animals show that tricyclic antidepressants may reduce β -adrenergic receptor responsiveness following chronic administration. In contrast, venlafaxine and ODV reduce β -adrenergic responsiveness after both acute (single dose) and chronic administration.

Venlafaxine has no significant affinity for rat brain muscarinic, H₁-histaminergic or α ₁-adrenergic receptors *in vitro*. Pharmacological activity at these receptors is potentially associated with various sedative, cardiovascular, and anticholinergic effects seen with other psychotropic drugs. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine also does not produce noradrenaline release from brain slices. It has no significant central nervous system (CNS) stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

Pharmacokinetics

Steady-state concentrations of venlafaxine and ODV 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/day. Mean \pm SD steady state plasma clearance of venlafaxine and ODV is 1.3 \pm 0.6 and 0.4 \pm 0.2 L/h/kg, respectively; apparent elimination half-life is 5 \pm 2 and 11 \pm 2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5 \pm 3.7 and 5.7 \pm 1.8 L/kg, respectively.

Absorption

On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed, indicating that absorption of venlafaxine is nearly complete. However, the pre-systemic metabolism of venlafaxine (which primarily forms the active metabolite, ODV) reduces the absolute bioavailability of venlafaxine to 42% \pm 15%.

After administration of EFEXOR-XR (150 mg q24 hours), the peak plasma concentrations (C_{\max}) of venlafaxine (150 ng/mL) and ODV (260 ng/mL) were attained within 6.0 ± 1.5 and 8.8 ± 2.2 hours, respectively. The rate of absorption of venlafaxine from the EFEXOR-XR capsule is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of EFEXOR-XR (15 ± 6 hours) is actually the absorption half-life instead of the true disposition half-life (5 ± 2 hours) observed following administration of an immediate-release tablet.

When equal doses of venlafaxine, administered either as an immediate-release tablet taken in divided doses or as a modified-release capsule, were taken once a day, the exposure (AUC, area under the concentration curve) to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the EFEXOR-XR capsule. Therefore, the EFEXOR-XR capsule provides a slower rate of absorption, but the same extent of absorption (i.e., AUC), as the venlafaxine immediate-release tablet.

No accumulation of venlafaxine or ODV has been observed during chronic administration in healthy subjects.

Distribution

The degree of binding of venlafaxine to human plasma proteins is $27\% \pm 2\%$ at concentrations ranging from 2.5 to 2215 ng/mL, and the degree of ODV binding to human plasma proteins is $30\% \pm 12\%$ at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with concomitantly administered venlafaxine are not expected. Following intravenous administration, the steady-state volume of distribution of venlafaxine is 4.4 ± 1.9 L/kg, indicating that venlafaxine distributes well beyond the total body water.

Metabolism

Following absorption, venlafaxine undergoes extensive pre-systemic metabolism in the liver. The primary metabolite of venlafaxine is ODV, but venlafaxine is also metabolised to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalysed by CYP2D6 and that the formation of N-desmethylvenlafaxine is catalysed by CYP3A3/4. The results of the *in vitro* studies have been confirmed in a clinical study with subjects who are CYP2D6-poor and -extensive metabolisers. However, despite the metabolic differences between the CYP2D6-poor and -extensive metabolisers, the total exposure to the sum of the two active species (venlafaxine and ODV) was similar in the two metaboliser groups. Therefore, CYP2D6-poor and -extensive metabolisers can be treated with the same regimen of EFEXOR-XR (see **INTERACTIONS WITH OTHER MEDICINES**, CYP2D6 Inhibitors).

Excretion

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours after a single radio-labelled dose as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

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

Food-Drug Interactions

Administration of EFEXOR-XR with food has no effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Subject age and sex do not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was probably caused by the decrease in renal function that typically occurs with aging.

In some patients with compensated hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered. The reduction in both the metabolism of venlafaxine and elimination of ODV resulted in higher plasma concentrations of both venlafaxine and ODV.

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and ODV was reduced, and $t_{1/2}$ was prolonged. The reduction in total clearance was most pronounced in subjects with creatinine clearance less than 30 mL/min.

CLINICAL TRIALS

Use in Major Depression

Three double blind, placebo controlled trials, of up to 12 weeks duration, have examined the clinical efficacy of EFEXOR-XR in the treatment of major depression. One of these studies also incorporated an active comparator, paroxetine. These studies showed EFEXOR-XR to have greater efficacy than both placebo and paroxetine in reducing depression.

Use in Generalised Anxiety Disorder

Five placebo-controlled trials were conducted to evaluate the efficacy of EFEXOR-XR in the treatment of anxiety. Two trials were eight-week studies, utilising EFEXOR-XR doses of 75 mg, 150 mg and 225 mg/day and of 75 mg and 150 mg/day. In one of these, buspirone was found not to be significantly different to placebo or to EFEXOR-XR. However, EFEXOR-XR was found to be superior to placebo. Two other trials were the first eight-weeks of two long term studies, utilising EFEXOR-XR doses of 75 mg-225 mg/day and of 37.5 mg, 75 mg and 150 mg/day.

Four studies demonstrated superiority of EFEXOR-XR over placebo on at least five of the following efficacy scales: HAM-A total score, the HAM-A psychic anxiety factor, the Hospital Anxiety and Depression (HAD) anxiety subscale, and the CGI severity of illness scale, as well as the HAM-A anxious mood and tension item. Two of these four studies continued for up to six months. These two studies, which utilised EFEXOR-XR doses of 75 mg-225 mg/day and 37.5 mg, 75 mg and 150 mg/day demonstrated superiority of EFEXOR-XR over placebo on the HAM-A total score, HAM-A psychic anxiety factor, the

HAD anxiety factor, and the CGI severity of illness scale, as well as the HAM-A anxious mood item.

The fifth trial was a short-term (8-week) comparison of the efficacy of 2 fixed doses of EFEXOR-XR (75 mg and 150 mg) with placebo and diazepam followed by a comparison of the long-term (6-month) efficacy of EFEXOR-XR and placebo in the prevention of relapse. The most important results were the primary efficacy variables at week 8 using an LOCF analysis. These demonstrated no significant differences between either venlafaxine and placebo, or diazepam and placebo for any of the primary efficacy variables. In view of this failure to demonstrate any effectiveness of either venlafaxine or diazepam over placebo, the long-term outcomes of this study are not of clinical or theoretical value. In conclusion, this study showed no anxiolytic effect of either diazepam or placebo in the short-term (8 week phase).

Baseline and Final Mean HAM-A Total and CGI Severity Scores for Placebo-Controlled GAD Studies

Study Number	----- HAM-A Total-----			----- CGI Severity -----		
	Treatment	n	Baseline	Final	n	Baseline
210 (8-week study)						
Placebo	96	24.1	14.7	96	4.4	3.2
Venlafaxine XR (mg)						
75	86	24.7	13.5	86	4.5	3.0
150	81	24.5	12.3	81	4.5	2.9
225	86	23.6	11.9	86	4.4	2.8
214 (8-week study)						
Placebo	98	23.7	15.4	98	4.3	3.3
Venlafaxine XR (mg)						
75	87	23.7	13.0	87	4.2	2.8
150	87	23.0	13.6	87	4.2	3.0
Bupirone	93	23.8	14.3	93	4.2	3.2
218 (6-month study)						
Placebo	123	24.9	16.2	123	4.4	3.5
Venlafaxine XR (mg)						
75-225	115	25.0	11.6	115	4.4	2.7
377 (8-week period)						
Placebo	96	27.7	15.1	89	4.8	3.2
Venlafaxine XR (mg)						
75	181	28.0	12.8	160	4.9	2.9
150	169	28.0	14.2	146	4.9	3.1
Diazepam	89	28.4	13.5	79	4.8	2.9
378 (6-month study)						
Placebo	129	26.7	15.6	129	4.6	3.2
Venlafaxine XR (mg)						
37.5	138	26.6	12.6	138	4.4	2.6
75	130	26.3	10.4	129	4.4	2.4
150	131	26.3	9.5	131	4.6	2.2

Depression Relapse/Recurrence

A long-term study of depressed outpatients who had responded to EFEXOR-XR during an initial 8-week open-label treatment phase and were randomly assigned to continuation on EFEXOR-XR or placebo for 6 months demonstrated a significantly lower relapse rate for patients taking EFEXOR-XR compared with those on placebo.

In a second long-term study, outpatients with a history of recurrent depression who had responded to EFEXOR (the immediate-release form of venlafaxine) by 8 weeks and maintained improvement during an initial 6-month open-label treatment phase were randomly assigned to maintenance therapy on EFEXOR or placebo for 12 months. Significantly fewer patients taking EFEXOR compared with those on placebo had a reappearance of depression.

Social Anxiety Disorder

The efficacy of EFEXOR-XR as a treatment for social anxiety disorder (also known as social phobia) was established in four double-blind, parallel-group, 12-week, multi-centre, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, fixed/flexible-dose study in adult outpatients meeting DSM-IV criteria for Social Anxiety Disorder. Patients received doses in a range of 75-225 mg/day. Efficacy was assessed with the Liebowitz Social Anxiety Scale (LSAS). The LSAS measures the relationship of impairment because of social anxiety disorder symptoms by evaluating a patient's fear and avoidance in a broad range of situations (i.e., 13 performance and 11 social interaction situations). Psychometric studies have shown the LSAS to be a valid and reliable measure of social anxiety.¹ The LSAS scale has also been shown to be sensitive to differences between active and placebo treatments.²

The results of these trials are presented in the table below. In these five trials, EFEXOR-XR was significantly more effective than placebo on change from baseline to endpoint on the LSAS total score.

¹ Clark DB, et al. Systematic assessment of social phobia in clinical practice. *Depress and Anxiety* 1997;6:47-61.

² Davidson JRT, et al. Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol.* 1993;13:423-428.

Summary of Results for Primary Efficacy Variable in ITT Patients at Final On-Therapy Visit: 12 week and 6 month

Variable Study Number Treatment Group	No. of Patients	Raw baseline Score	Adjusted Final On-therapy Score	Adjusted Mean Change from Baseline	p-value vs. Placebo
Short-term (12 week) Studies					
LSAS					
Study 1					
Placebo	138	86.7	69.0	-19.9	
Venlafaxine XR ^a	133	91.1	57.8	-31.0	<0.001
Study 2 ^b					
Placebo	135	87.4	66.9	-22.1	
Venlafaxine XR ^a	126	90.8	56.3	-32.8	0.003
Study 3					
Placebo	132	83.6	64.5	-19.1	
Venlafaxine XR ^a	129	83.2	47.6	-36.0	<0.001
Paroxetine ^c	128	83.9	48.1	-35.4	<0.001
Study 4					
Placebo	144	86.1	64.3	-22.2	
Venlafaxine XR	133	86.2	51.5	-35.0	<0.001
Paroxetine	136	87.2	47.3	-39.2	<0.001
Long-term (6 month) Study					
LSAS					
Study 5					
Placebo	126	89.3	65.6	-23.5	
Venlafaxine XR (total) ^d	238	89.0	51.2	-37.8	<0.001
Venlafaxine XR 75mg	119	91.8	51.0	-38.1	<0.001
Venlafaxine 150-225mg	119	86.2	51.5	-37.6	<0.001

a: Flexible dose range for venlafaxine XR was 75-225mg/day; b: Data shown are for ITT population; c: Flexible dose range for paroxetine was 20-50mg/day; d: Primary treatment group. Abbreviations: ITT = intent to treat; LSAS = Liebowitz Social Anxiety Scale

Panic Disorder

The efficacy of EFEXOR-XR capsules as a treatment for panic disorder was established in two double-blind, 12-week, multicentre, placebo-controlled studies in adult outpatients meeting DSM-IV criteria for panic disorder, with or without agoraphobia. Patients received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study.

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) in the Clinical Global Impressions (CGI) Improvement scale. In these two trials, EFEXOR-XR was significantly more effective than placebo in all three variables.

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, adult outpatients meeting DSM-IV criteria for panic disorder who had responded during a 12-week open phase with EFEXOR-XR (75 to 225 mg/day) were randomly assigned to continue the same EFEXOR-XR dose (75, 150, or 225 mg) or switch to

placebo for observation for relapse during a 6-month double-blind phase. 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. Patients receiving continued EFEXOR-XR treatment experienced significantly lower relapse rates over the subsequent 6 months compared with those receiving placebo.

INDICATIONS

EFEXOR-XR is indicated for the treatment of:

- Major Depression
- Generalised Anxiety Disorder
- Social Anxiety Disorder
- Panic Disorder.

EFEXOR-XR is also indicated for the prevention of relapse and recurrence of major depression where appropriate.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine or any excipients in the formulation.

Concomitant use of venlafaxine and any monoamine oxidase inhibitor- (MAOI) is contraindicated. EFEXOR-XR must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. EFEXOR-XR must be discontinued for at least 7 days before starting treatment with any MAOI - (See **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidality (suicidal ideation and behaviours) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, all patients treated with venlafaxine should be monitored appropriately and observed closely for clinical

worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

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

Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depression as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and /or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who exhibit the above symptoms or whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms (see also **Abrupt Discontinuation of EFEXOR-XR**).

Prescriptions for EFEXOR-XR should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the possibility of overdose.

Information for Patients and Caregivers

Patients, their families and their caregivers should be encouraged to be alert for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms (see also **Use in Children and Adolescents**).

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

Serotonin Syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life threatening condition, or Neuroleptic Malignant Syndrome (NMS)-like reactions may occur with venlafaxine

treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans), with drugs that impair metabolism of serotonin (including MAOIs, such as methylene blue), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, confusion, hallucinations, and coma), autonomic instability (e.g. diaphoresis, tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination, myoclonus, tremor), and/or gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhoea). Serotonin syndrome, in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes.

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

Treatment with EFEXOR-XR should be discontinued if serotonin syndrome or NMS-Like reactions occur and supportive symptomatic treatment initiated.

The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see also **INTERACTIONS WITH OTHER MEDICINES**).

Bone Fractures

Epidemiological studies show an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors (SRIs) including venlafaxine. The mechanism leading to this risk is not fully understood.

Mydriasis

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

Use in Patients with Renal Impairment

The total daily dose of venlafaxine should be reduced by 25% to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min.

The total daily dose of venlafaxine should be reduced by 50% in haemodialysis patients.

Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Use in Patients with Hepatic Impairment

The total daily dose of venlafaxine should be reduced by 50% in patients with mild to moderate hepatic impairment. Reductions of more than 50% may be appropriate for some patients.

Because of individual variability in clearance in these patients, individualisation of dosage may be desirable

Sustained Hypertension

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine.

Among patients treated with 75 to 375 mg per day of EFEXOR-XR in pre-marketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) \geq 90 mm Hg and \geq 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5 to 225 mg per day of EFEXOR-XR in pre-marketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3 to 7% at 100 to 300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of EFEXOR-XR over 300 mg per day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled pre-marketing depression studies with EFEXOR-XR 75 to 225 mg per day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for EFEXOR-XR treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled pre-marketing GAD studies with EFEXOR-XR 37.5 to 225 mg per day up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for EFEXOR-XR treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In pre-marketing Social Anxiety Disorder studies up to 12 weeks, the final on-therapy mean change from baseline in SDBP was small - an increase of 0.78 mmHg, compared to a decrease of 1.41 mmHg in placebo-treated patients. In a 6-month study, the final on-therapy mean increase from baseline in SDBP with EFEXOR-XR 150 to 225 mg was 1.49 mmHg. The increase was significantly different from the 0.6 mmHg decrease with placebo and the 0.2 mmHg decrease with EFEXOR-XR 75 mg.

In pre-marketing depression studies, 0.7% (5/705) of the EFEXOR-XR treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In pre-marketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the EFEXOR-XR treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months).

Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience.

Sustained increases of SDBP could have adverse consequences. Therefore it is recommended that patients receiving EFEXOR-XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Increase in Serum Cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5.3% of EFEXOR immediate release tablet-treated patients and 0.0% of placebo-treated patients for at least 3 months in placebo-controlled clinical trials.

Treatment with EFEXOR-XR for up to 12 weeks in pre-marketing placebo-controlled depression trials was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 0.039 mmol/L (1.5 mg/dL). EFEXOR-XR treatment for up to 8 weeks and up to 6 months in pre-marketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 0.026 mmol/L (1.0 mg/dL) and 0.059 mmol/L (2.3 mg/dL), respectively.

In the 12 week Social Anxiety Disorder studies, small mean increases in fasting levels of total cholesterol (0.20 mmol/L, 4%) were seen in the EFEXOR-XR-treated group at the final on-therapy evaluation; the increases were significantly different from the changes in the placebo group. In a 6-month study, the final on-therapy mean increase in total cholesterol was higher (0.32 mmol/L, 7%) in the EFEXOR-XR 150 to 225 mg group; however the total cholesterol value was only slightly increased (0.01 mmol/L) for the EFEXOR-XR 75 mg group.

There were also significant mean increases from baseline in LDL, but not HDL for the EFEXOR-XR 150 to 225 mg group. The final on-therapy increase of 0.213 mmol/L from baseline in LDL with EFEXOR-XR 150 to 225 mg was significantly different from the small decrease with placebo (0.079 mmol/L) and the negligible increase with EFEXOR-XR 75 mg (0.006 mmol/L).

Measurement of serum cholesterol levels should be considered during long-term treatment.

Hyponatraemia

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

Caution is advised in administering EFEXOR-XR to patients with diseases or conditions that could affect haemodynamic responses or metabolism.

Myocardial Infarction and Unstable Heart Disease

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

Patients with these diagnoses were systematically excluded from any clinical studies during the product's trials.

Evaluation of the electrocardiograms for 769 patients who received immediate release EFEXOR in 4 to 6-week double blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

The electrocardiograms for patients who received EFEXOR-XR or placebo in the depression GAD and Social Anxiety Disorder trials were analysed. The mean change from baseline in corrected QT interval (QTc) for EFEXOR-XR treated patients in depression studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for EFEXOR-XR and decrease of 1.9 msec for placebo). The mean change from baseline QTc for EFEXOR-XR treated patients in the GAD studies did not differ significantly from placebo. The final on-therapy mean increase from baseline in QTc (3 msec) was significant for EFEXOR-XR treated patients in the Social Anxiety Disorder short-term studies. In the 6 month study, the final on-therapy mean increase from baseline in QTc with EFEXOR-XR 150 to 225 mg (3 msec) was significant, but the increase was not significantly different from the small mean increase (0.5 msec) with placebo. The value for EFEXOR-XR 75 mg was a 0.05 msec decrease.

Increases in heart rate may occur, particularly with higher doses. Therefore caution is advised in patients whose underlying conditions may be compromised by increases in heart rate.

The mean change from baseline in heart rate for EFEXOR-XR treated patients in both the GAD and depression studies was significantly higher than for placebo (a mean increase of 3-4 beats per minute for EFEXOR-XR and 0-1 beat per minute for placebo in the GAD and depression studies respectively). In the pooled short-term Social Anxiety Disorder studies, the final on-therapy mean increase from baseline in heart rate with EFEXOR-XR was 5 beats per minute. In the 6 month study, the final on-therapy mean increases from baseline in heart rate were significant with EFEXOR-XR 75 (2 beats per minute) and EFEXOR-XR 150 to 225 mg (6 beats per minute); however only the increase with the higher dose was significantly different from the small increase with placebo (0.4 beats per minute). The clinical significance of these changes is unknown.

Abrupt Discontinuation of EFEXOR-XR

Discontinuation effects are well known to occur with antidepressants. Discontinuation symptoms have been assessed both in patients with depression and in those with anxiety. Abrupt discontinuation, dose reduction, or tapering of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment.

Symptoms reported included agitation, anorexia, anxiety, confusion, dry mouth, fatigue, paraesthesias, vertigo, hypomania, nausea, vomiting, dizziness, convulsion, headache, diarrhoea, sleep disturbance, insomnia, somnolence, sweating and nervousness. Where such symptoms occurred, they were usually self-limiting, but in a few patients lasted for several weeks.

There is also a report of a withdrawal syndrome, confirmed by two challenges in a 32-year-old woman who had received venlafaxine 300 mg daily for 8 months. It is, therefore, recommended that the dosage of EFEXOR-XR be tapered gradually and the patient monitored. The period required for discontinuation may depend on the dose, duration of therapy and the individual patient (See **DOSAGE AND ADMINISTRATION** and **ADVERSE EVENTS**).

Altered Weight

Weight changes, either losses or gains, do not appear to present a clinically important feature of venlafaxine treatment. Clinically significant weight gain or loss was seen in less than 1% of patients treated with venlafaxine during clinical trials. A dose-dependent weight loss (mean loss <1 kg) was noted in some patients treated with venlafaxine during the first few months of venlafaxine treatment. After month 9, the mean weight began to increase slightly but significantly, an effect often seen with tricyclic antidepressant therapy. Significant weight loss (> 7 kg) was seen in 6 (0.3%) of 2,181 patients, compared to no patients treated with placebo and 0.2% of patients treated with a comparative antidepressant.

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

Seizures

Seizures may occur with venlafaxine therapy. EFEXOR-XR, as with all antidepressants, should be introduced with care, in patients with a history of seizure disorders. EFEXOR-XR should be discontinued in any patient who develops seizures.

Mania/Hypomania and Bipolar Disorder

Mania/hypomania may occur in a small proportion of patients with mood disorders treated with antidepressants, including venlafaxine.

Venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

A major depressive episode may be the initial presentation of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that EFEXOR-XR is not approved for use in treating bipolar depression.

Aggression may occur in a small proportion of patients who have received antidepressants, including venlafaxine treatment, dose reduction or discontinuation.

Venlafaxine should be used cautiously in patients with a history of aggression.

Skin/Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or related allergic phenomena

Skin and Mucous Membrane Bleeding

Drugs that inhibit serotonin uptake may lead to abnormalities of platelet aggregation. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking venlafaxine, particularly if predisposed to such events.

Venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

Effects on Cognitive and Motor Performance

Although venlafaxine has been shown not to affect psychomotor, cognitive or complex behaviour performance in healthy volunteers, any psychoactive medication may impair judgment, thinking or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the treatment does not affect them adversely.

Physical and Psychological Dependence

Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely observing them for signs of misuse or abuse of venlafaxine (e.g. development of tolerance, increase in dose, drug-seeking behaviour) (see **PHARMACOLOGY**).

Use in Elderly Patients

No overall differences in effectiveness or safety were observed between elderly (aged 65 years and older) and younger patients. EFEXOR-XR does not appear to pose any exceptional safety problems for healthy elderly patients.

Effectiveness in elderly patients with social anxiety disorder has not been established.

Use in Children and Adolescents

Safety and effectiveness in individuals below 18 years of age have not been established. Efexor-XR should not be used in such patients.

As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol have been observed in children and adolescents aged 6 to 17 years.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depression (16 trials), obsessive compulsive disorder (4 trials) and other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depression trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The 9 antidepressant medicines in the pooled analyses included 5 SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and 4 non-SSRIs

(bupropion, mirtazapine, nefazodone, venlafaxine) (see also **Clinical Worsening and Suicide Risk** and **ADVERSE EVENTS**).

Use in Pregnancy

Category: B2

The safety of venlafaxine in human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh the possible risks. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

Some neonates exposed to venlafaxine, other SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, or tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, 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.

Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for venlafaxine treatment remains unknown.

Some epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

In a rat teratology study, venlafaxine was given orally at dosages up to 80 mg/kg/day (approximately 11 times the maximum recommended human dose). Foetotoxicity evidenced by growth retardation was slightly increased at 80 mg/kg/day, an effect which may be related to maternal toxicity at this dose level. Foetal survival and morphologic development were not affected. In another teratology study, rabbits were given venlafaxine dosages up to 90 mg/kg/day. Foetotoxicity evidenced by resorption and foetal loss was slightly increased at 90 mg/kg/day (approximately 12 times the maximum recommended human dose). These effects could be correlated with maternal toxicity. No venlafaxine-associated teratogenic effect was noted in either species at any dosage, though there was an increased incidence of 'W'-shaped apex of the heart in the rabbit study. In these studies, animal exposure to the main human metabolite ODV was less, and estimated exposure to venlafaxine was approximately 6-fold more than would be expected in humans taking the recommended therapeutic and maximum doses. In rats, estimated exposure to venlafaxine was more than the expected human exposure. No teratogenic effect was seen.

In a perinatal toxicity study in rats after oral dosing of dams with 30 mg/kg or more, decreased pup survival following birth was observed. This effect is secondary to treatment-decreased maternal care, and is also seen with other antidepressants.

Use in Lactation

Venlafaxine and/or its metabolites are secreted in milk of lactating rats at concentrations higher than those found in the plasma of the dam. Venlafaxine and its metabolites have been shown to pass into human milk. The total dose of venlafaxine and O-desmethylvenlafaxine ingested by breast fed infants can be as high as 9.2% of maternal intake. Therefore, the use of EFEXOR-XR in nursing women cannot be recommended. Exposed infants should be observed closely.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m² basis.

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

Venlafaxine was given by oral gavage to mice and rats for 18 months and 24 months respectively, at dosages up to 120 mg/kg/day. There were no clear drug-related oncogenic effects in either species. In these studies, animal exposure to the main human metabolite ODV was less, and exposure to venlafaxine was more than would be expected in humans taking the recommended therapeutic and maximum doses.

There was no evidence of gene mutation or chromosomal change in a series of genotoxicity assays using venlafaxine and the main human metabolite ODV.

Signs of pharmacologic toxicity were seen in paternal and maternal rats given venlafaxine doses of 30 and 60 mg/kg/day, but no adverse effect was noted in fertility or general reproductive performance. Decreased foetal size and pup weight at birth with 60 mg/kg/day may be correlated with maternal toxicity.

INTERACTIONS WITH OTHER MEDICINES

Venlafaxine and ODV are 27% and 30% bound to plasma proteins respectively, therefore interactions due to protein binding of venlafaxine and the major metabolite are not expected.

Monoamine oxidase inhibitors

Concomitant use with EFEXOR-XR is contraindicated.

Irreversible Monoamine Oxidase Inhibitors

Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior to initiation of a MAOI or when these two agents are co-administered. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome and/or serotonergic syndrome, seizures, and death. Do not use EFEXOR-XR in combination with a

MAOI or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping EFEXOR-XR before starting a MAOI (see **CONTRAINDICATIONS**).

Reversible Monoamine Oxidase Inhibitors

EFEXOR-XR should not be administered concomitantly with moclobemide.

There are no clinical trials to support the recommendation of a specific time between discontinuing treatment with the reversible MAOI, moclobemide and initiating EFEXOR-XR therapy or switching to moclobemide. Given the risk for adverse reactions described for irreversible MAOIs (see above), an adequate washout period should be ensured when switching a patient between EFEXOR-XR and moclobemide. The appropriate washout period should take into account the pharmacological properties of venlafaxine and moclobemide and the clinician's assessment of the individual patient. Based on the half-lives of moclobemide, venlafaxine and ODV, the minimum washout period should be 24 hours when switching from moclobemide to EFEXOR-XR and 7 days when switching from EFEXOR-XR to moclobemide.

CNS Active Drugs

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

As with other serotonergic agents, serotonin syndrome, a potentially life threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St John's Wort [*Hypericum perforatum*]), with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI] and methylene blue), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms. (See **PRECAUTIONS**)

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

As with other antidepressants, co-administration of EFEXOR-XR and products containing St. John's Wort (*Hypericum perforatum*) is not recommended due to possible pharmacodynamic interactions.

No information is available on the use of EFEXOR-XR in combination with opiates.

There have been reports of elevated clozapine levels in association with adverse events including seizures, following the administration of venlafaxine.

Indinavir

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

Ethanol

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

Cimetidine

At steady-state cimetidine has been shown to inhibit the first-pass metabolism of venlafaxine but had no apparent effect on the formation or elimination of ODV, which is present in much greater quantity in the systemic circulation. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. No dosage adjustment seems necessary when EFEXOR-XR is co-administered with cimetidine. However, for elderly patients or patients with hepatic dysfunction, the interaction could potentially be more pronounced and for such patients clinical monitoring is indicated when EFEXOR-XR is administered with cimetidine.

Diazepam.

The pharmacokinetic profiles of venlafaxine and ODV were not altered when venlafaxine and diazepam were administered together to healthy volunteers. Venlafaxine had no effect on the pharmacokinetics of diazepam or affect the psychomotor and psychometric effects induced by diazepam.

Lithium

The steady-state pharmacokinetics of venlafaxine and ODV are not affected when lithium is co-administered. Venlafaxine also has no effect on the pharmacokinetics of lithium. (See also **CNS Active Drugs**.) However, there have been reports of venlafaxine interaction with lithium resulting in increased lithium levels.

Haloperidol

Venlafaxine administered under steady-state conditions (75 mg twice daily) to 24 healthy subjects decreased total oral clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{\max} increased 88% when co-administered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

Metoprolol

Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) to healthy volunteers in a pharmacokinetic interaction

study for both drugs resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α -hydroxymetoprolol. Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, ODV. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Risperidone

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

Drugs Metabolised by Cytochrome P450 Isoenzymes

In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6 and that venlafaxine does not inhibit CYP1A2, CYP2C9 or CYP3A4. Some of these findings have been confirmed with drug interaction studies between venlafaxine and imipramine (metabolised by CYP2D6) and diazepam (metabolised by CYP2C19). Therefore, EFEXOR-XR is not expected to interact with other drugs metabolised by these isoenzymes.

Imipramine

Venlafaxine did not affect the CYP2D6-mediated 2-hydroxylation of imipramine or its active metabolite, desimipramine, which indicates that venlafaxine does not inhibit the CYP2D6 isoenzyme. However, the renal clearance of 2-hydroxydesimipramine was reduced with co-administration of venlafaxine.

Imipramine partially inhibited the CYP2D6-mediated formation of ODV, however, the total concentrations of active compounds (venlafaxine plus ODV) was not affected with imipramine administration. Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolisers, the total sum of the two active species (venlafaxine and ODV) was similar in the two metaboliser groups. Therefore, no dosage adjustment is expected when venlafaxine is co-administered with a CYP2D6 inhibitor. However, desipramine AUC, C_{max} , and C_{min} increased by about 35% in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2.5 to 4.5 fold. The clinical significance of this finding is unknown.

Potential for Other Drugs to Affect Venlafaxine

The metabolic pathways for venlafaxine include CYP2D6 and CYP3A4.

In vitro and *in vivo* studies indicate that venlafaxine is metabolised predominantly to its active metabolite ODV by the cytochrome P450 enzyme CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism (such as amiodarone and quinidine) and venlafaxine. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine.

CYP2D6 Inhibitors

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

CYP3A4 Inhibitors.

Concomitant use of CYP3A4 inhibitors (such as erythromycin, fluconazole, ketoconazole and grapefruit juice) and venlafaxine may increase levels of venlafaxine and ODV. Therefore caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

In vitro studies indicate that venlafaxine is likely metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. A pharmacokinetic study with ketoconazole (a CYP3A4 inhibitor) in extensive (EM) and poor metabolisers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and ODV in most subjects following administration of ketoconazole. Venlafaxine C_{max} increased by 26% in EM subjects and 48% in PM subjects. C_{max} values for ODV increased by 14% and 29% in EM and PM subjects, respectively. Venlafaxine AUC increased by 21% in EM subjects and 70% in PM subjects. AUC values for ODV increased by 23% and 33% in EM and PM subjects, respectively.

CYP2D6 and 3A4 Inhibitors

The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolising enzymes for venlafaxine, has not been studied. However, this concomitant use would be expected to increase venlafaxine plasma concentrations. Therefore caution is advised if a patient's therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems.

Antihypertensive and Hypoglycaemic Agents

Retrospective analysis of study events occurring in patients taking venlafaxine concurrently with antihypertensive or hypoglycaemic agents in clinical trials provided no evidence suggesting incompatibility between treatment with venlafaxine and treatment with either antihypertensive or hypoglycaemic agents.

Electroconvulsive Therapy

There are no clinical data establishing the benefit of EFEXOR-XR combined with electroconvulsive therapy.

Effects on Laboratory Tests

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.

ADVERSE EVENTS

Adverse events are listed in the following table in CIOMS frequency categories:

Common: $\geq 1\%$; Uncommon: $\geq 0.1\%$ and $< 1\%$; Rare: $\geq 0.01\%$ and $< 0.1\%$; Very rare: $< 0.01\%$.

Body System	ADVERSE EVENTS
<i>Body As A Whole</i>	
Common:	Asthenia/fatigue, chills.
Uncommon:	Photosensitivity reaction.
Very rare:	Anaphylaxis.
<i>Cardiovascular</i>	
Common:	Hypertension, vasodilatation (mostly hot flashes/flushes), palpitations
Uncommon:	Hypotension, postural hypotension, syncope, tachycardia.
Very rare:	QT prolongation, ventricular fibrillation, ventricular tachycardia (including torsade de pointes).
<i>Digestive</i>	
Common:	Appetite decreased, constipation, nausea, vomiting, gastrointestinal bleeding
Uncommon:	Bruxism, diarrhoea.
Very rare:	Pancreatitis.
<i>Haematological/Lymphatic</i>	
Uncommon:	Ecchymosis, mucous membrane bleeding.
Rare:	Prolonged bleeding time, thrombocytopenia.
Very rare:	Blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia)
<i>Metabolic/Nutritional</i>	
Common:	Serum cholesterol increased (particularly with prolonged administration and with higher doses), weight loss.
Uncommon:	Abnormal liver function tests, hyponatraemia, weight gain.
Rare:	Hepatitis, syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Very rare:	Prolactin increased
<i>Musculoskeletal</i>	
Very rare:	Rhabdomyolysis.
<i>Nervous</i>	
Very Common:	Headache
Common:	Abnormal dreams, decreased libido, dizziness, dry mouth, increased muscle tonus, insomnia, nervousness, paraesthesia, sedation, tremor, confusion, depersonalisation
Uncommon:	Apathy, hallucinations, myoclonus, agitation, impaired coordination and balance.
Rare:	Akathisia/psychomotor restlessness, convulsion, manic reaction, neuroleptic malignant syndrome (NMS), serotonergic syndrome.
Very rare:	Delirium, extrapyramidal reactions (including dystonia and dyskinesia), tardive dyskinesia.
<i>Respiratory</i>	
Common:	Yawning.
Uncommon:	Dyspnoea
Very rare:	Pulmonary eosinophilia.
<i>Skin</i>	
Common:	Sweating (including Night Sweats).
Uncommon:	Rash, alopecia.
Very Rare:	Erythema multiforme, Stevens-Johnson syndrome, pruritus, urticaria.

Body System

Frequency Unknown:

Special Senses

Common:

Uncommon:

Very rare:

Urogenital

Common:

Uncommon:

Rare:

Injury, poisoning and procedural complications

Not known

ADVERSE EVENTS

Toxic epidermal necrolysis

Abnormality of accommodation, mydriasis, visual disturbance.

Altered taste sensation, tinnitus.

Angle closure glaucoma.

Abnormal ejaculation/orgasm (males), anorgasmia, erectile dysfunction, urination impaired (mostly hesitancy), menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Urinary frequency increased

Abnormal orgasm (females), urinary retention, proteinuria.

Urinary incontinence.

Bone fracture

Discontinuation effects are well known to occur with antidepressants, and it is therefore recommended that the dosage is tapered gradually and the patient monitored (see **DOSAGE AND ADMINISTRATION**). The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of treatment: hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea, and vomiting. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

In the Social Anxiety Disorder pooled short-term studies, the most common taper/post-study-emergent adverse events were dizziness (13%), nausea (7%), insomnia (3%), nervousness (3%) and asthenia (2%). In the 6-month study, the most common taper/post-study treatment emergent adverse events were dizziness (21% and 16%) and nausea (7% and 10%) for EFEXOR-XR 75 mg and EFEXOR-XR 150-225 mg, respectively.

Paediatric Patients (see PRECAUTIONS - Use in Children and Adolescents)

In general, the adverse reaction profile of venlafaxine in placebo-controlled clinical trials in children and adolescents (aged 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. Particularly, the following adverse reactions were observed: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis and myalgia.

In paediatric clinical trials, there were increased reports of hostility and, especially in major depression, suicide-related adverse events such as suicidal ideation and self-harm.

DOSAGE AND ADMINISTRATION

Usual Dose

The usual recommended dose for the treatment of major depression, generalised anxiety disorder or social anxiety disorder is 75 mg per day given once daily. After two weeks, the dose may be increased to 150 mg per day given once daily if further clinical improvement is

required. If needed, this can be increased up to 375 mg given once daily. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days.

Antidepressant activity with the 75 mg dose was observed after 2 weeks of treatment and anxiolytic activity was observed after one week.

It is recommended that EFEXOR-XR be taken with food, at approximately the same time every day. Each capsule must be swallowed whole with fluid. Do not divide, crush, chew or dissolve.

Panic Disorder

The recommended dose is 75 mg of EFEXOR-XR once daily. Treatment should be started with a dose of 37.5 mg per day of EFEXOR-XR for the first 4 to 7 days, after which the dose should be increased to 75 mg once daily.

Patients not responding to the 75 mg/day dose may benefit from dose increases to a maximum of 225 mg/day. Dosage increases can be made in increments of 75 mg per day at intervals of approximately 2 weeks or more, but not less than 4 days.

Patients with Renal or Hepatic Impairment

Patients with renal and/or hepatic impairment should receive lower doses of EFEXOR-XR. The total daily dose of venlafaxine should be reduced by 25% to 50% for patients with renal impairment with a glomerular filtration rate (GFR) of 10 to 70 mL/min. Haemodialysis clearances of both venlafaxine and ODV in humans are low. The total daily dose of venlafaxine should be reduced by 50% in haemodialysis patients.

Patients with mild to moderate hepatic impairment should also have their dosage reduced by 50%. Further reductions in dosage should be considered for patients with more severe degrees of hepatic impairment.

Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Elderly Patients

No adjustment in the usual dose is recommended for elderly patients solely because of their age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualising the dosage, extra care should be taken when increasing the dose.

Use in Children and Adolescents (under 18 years of age)

Safety and efficacy have not been established in this population. Consequently, EFEXOR-XR should not be used in patients under 18 years of age (see **PRECAUTIONS – Use in Children and Adolescents**).

Maintenance/Continuation/Extended Treatment

The physician should periodically re-evaluate the usefulness of long-term EFEXOR-XR treatment for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during initial treatment. Patients should be regularly re-assessed in order to evaluate the benefit of long-term therapy.

In Social Anxiety Disorder, continuing therapeutic benefit has been established for periods of up to 6 months. The need for continuing medication in patients with Social Anxiety Disorder who improve with EFEXOR-XR treatment should be periodically assessed.

Discontinuing EFEXOR-XR

When EFEXOR-XR at a dose of 75 mg/day or greater has been administered for more than 1 week is stopped, it is recommended whenever possible that the dose be tapered gradually to minimise the risk of discontinuation symptoms. In clinical trials with EFEXOR-XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. To facilitate tapering below 75 mg of EFEXOR-XR, physicians may consider prescribing the 37.5 mg capsules once daily (see also **Usual Dose** above). The period required for tapering may depend on the dose, duration of therapy, and the individual patient. Patients should be advised to consult their physician before abruptly discontinuing EFEXOR-XR.

OVERDOSAGE

In managing overdose, consider the possibility of multiple medication involvement. The physician should consider contacting a poison control centre on the treatment of any overdose. (See **INTERACTIONS WITH OTHER MEDICINES**).

During pre-marketing trials, most patients who have overdosed with venlafaxine were asymptomatic. Of the remainder, somnolence was the most commonly reported symptom. Mild sinus tachycardia and mydriasis have also been reported. There were no reports of seizures, respiratory distress, significant cardiac disturbances, or significant laboratory test result abnormalities among any of the cases reported to date. However, seizures and respiratory distress occurred in one patient in an on-going study who ingested an estimated 2.75g of venlafaxine with naproxen and thyroxine. Generalised convulsions and coma resulted and emergency resuscitation was required. Recovery was good without sequelae.

In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Other events reported include electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death. Serotonin toxicity has been reported in association with venlafaxine overdose.

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

Management of Overdosage

General supportive and symptomatic measures are recommended. Ensure an adequate airway, oxygenation and ventilation. Cardiac rhythm and vital signs must be monitored. Administration of activated charcoal may also limit drug absorption. Where there is a risk of aspiration, induction of emesis is not recommended. No specific antidotes for venlafaxine are known. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. Venlafaxine and ODV are not considered dialyzable because haemodialysis clearance of both compounds is low.

PRESENTATION

EFEXOR-XR modified release capsules are available for oral use as:

37.5 mg, grey cap/peach body with 'W' on the cap and "37.5" on the body.

75 mg, peach cap and body with 'W' on the cap and "75" on the body.

150 mg, dark orange cap and body with 'W' on the cap and "150" on the body.

EFEXOR-XR 37.5 mg, 75 mg and 150 mg are packed in blister packs in pack sizes of 7, 14 and 28.

Not all presentations are available.

Storage

Store below 30°C.

POISON SCHEDULE

PRESCRIPTION ONLY MEDICINE

NAME AND ADDRESS

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

DATE OF PREPARATION

12 June 2012

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