Product Summary

1. Trade Name of the Medicinal Product

Efexor 50mg

2. Qualitative and Quantitative Composition

Efexor 50mg tablet contains 50mg of venlafaxine as hydrochloride.

3. Pharmaceutical Form

Tablet

Efexor are peach coloured, shield-shaped tablets impressed with the '50' and embossed with a'W' on one side, and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Major depressive disorder

Efexor is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response Efexor is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and Method of Administration

Treatment with Efexor XL should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Efexor XL should be taken with food. Each capsule should be swallowed whole with fluid. Do not divide, crush, chew, or place the capsule in water. Efexor XL should be taken once daily, at approximately the same time, either in the morning or in the evening.

Depression:

The recommended dose is 75 mg per day given once daily. Most patients respond to this dose.

If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150 mg per day given once daily. There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.

In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased to the maximum recommended dose of Efexor XL capsules, 225 mg given once daily. In those more severely depressed or hospitalised patients who require daily venlafaxine doses of 300 mg or more, treatment with Efexor tablets should be initiated under specialist supervision including shared care arrangements.

The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).

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

75 mg *Generalised Anxiety Disorder (GAD):*

The recommended dose for GAD for Efexor XL is 75 mg, given once daily.

Patients should be reviewed at regular intervals and treatment should be discontinued after 8 weeks if there is no evidence of clinical response.

Depressed patients who are currently being treated with Efexor Tablets may be switched to Efexor XL. For example, a patient receiving Efexor Tablets 37.5 mg b.d. would receive Efexor XL 75 mg o.d. When switching, individual dosage adjustments may be necessary.

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

Patients at increased risk for suicide (see also sections 4.4 and 4.9):

Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.4 and 4.9) and a limited number of capsules should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.

Patients with Renal or Hepatic Impairment:

For patients with mild renal impairment (GFR >30ml/minute) no change in dosage is necessary. For patients with moderate renal impairment (GFR 10-30ml/minute), the dose should be reduced by 50%.

For patients with mild to moderate hepatic impairment, the dose should be reduced by 50%. Reductions of more than 50% may be appropriate for some patients. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Insufficient data are available to support the use of Efexor XL in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment.

Elderly Patients:

No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

Children/Adolescents:

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Efexor XL in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects).

The efficacy and safety of Efexor XL for other indications in children and adolescents under the age of 18 have not yet been established.

Maintenance/Continuation/Extended Treatment:

The physician should periodically re-evaluate the usefulness of long-term treatment with Efexor XL for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Efexor XL has been shown to be efficacious during long-term (up to 12 months) treatment.

In clinical trials venlafaxine was demonstrated to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

75 mg There is no evidence of efficacy for Efexor XL in GAD beyond 6 months. However, patients with GAD often suffer over many years and such patients may require long-term treatment.

Withdrawal symptoms seen on discontinuation of venlafaxine

Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75 mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

4.3 Contra-indications

1. Known hypersensitivity to venlafaxine or any other component of the product.

2. Concomitant use of venlafaxine with monoamine oxidase inhibitors *(See Interactions with other Medicaments and Other Forms of Interaction*s).

3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).

4. Efexor should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder *(see section 4.8 Undesirable Effects).*

4.4 Special Warnings and Special Precautions for Use

1. **Suicide/suicidal thoughts or clinical worsening**

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which venlafaxine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

2. **Withdrawal symptoms seen on discontinuation of venlafaxine treatment**
   Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 31% of patients treated with venlafaxine and in approximately 17% of placebo patients. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

   Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that venlafaxine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, Efexor should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression.

5. **Psychomotor restlessness:** The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of venlafaxine.

6. **Patients with cardiac disease.** Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated.

7. Significant electrocardiogram findings were observed in 0.8% of venlafaxine-treated patients compared with 0.7% of placebo-treated patients. Significant

changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

8. Dose-related increases in blood pressure have been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. 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 (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Efexor should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency Efexor should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. In clinical trials the mean heart rate was increased by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intra-ocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other

bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

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

18. The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Co-administration of venlafaxine and weight loss agents is not recommended. Venlafaxine is not indicated for weight loss alone or in combination with other products.
19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

MAOIs: Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Efexor in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Efexor before starting an MAOI (see also Contra-indications).

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

Lithium: Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

Imipramine/desipramine: The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and C_{max} were increased by approximately 35%.

Haloperidol: In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal

clearance, a 70% increase in AUC and an 88% increase in C_{max} for haloperidol. The elimination half-life remained unchanged.

Diazepam: The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.

Clozapine: Increased levels of clozapine, that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

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

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolisers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Efexor is co-administered with cimetidine. 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 is administered with cimetidine.

Warfarin: Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin following the addition 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 not known.

4.6 Pregnancy and Lactation

There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Efexor should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on Ability to Drive and Use Machines

Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable Effects

See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm.

The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common (<1/10 and >1/100); uncommon (<1/100 and >1/1000); rare (<1/1000); very rare (<1/10,000):

Blood and lymphatic system disorders - Uncommon**:** ecchymosis, mucous membrane bleeding; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (*see Special Warnings and Special Precautions for Use*) - Common: hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, ventricular fibrillation.

Gastrointestinal disorders - Very common: constipation, nausea (see below); Common: anorexia, appetite decreased**,** diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

General disorders - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: **anaphylaxis**

Metabolic and nutritional disorders - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses *(see Special Warnings and Special Precautions for Use*), weight gain or loss; Uncommon: hyponatraemia including SIADH *(see Special Warnings and Special Precautions for Use),* increased liver enzymes *(see below);* Rare: hepatitis; Very rare: prolactin increased.

Musculo-skeletal disorders - Common: arthralgia, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

Neurological disorders - Very common: dizziness, dry mouth, insomnia, nervousness, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, mania or hypomania *(see Special Warnings and Special Precautions for Use),* neuroleptic malignant syndrome-like effects, seizures *(see below and Special Warnings and Special Precautions for Use),* serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia**,** psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

Renal and urinary disorders - Common: urinary frequency; Uncommon: urinary retention.

Reproductive and breast disorders - Very common: anorgasmia**,** erectile dysfunction**,** abnormal ejaculation/orgasm; Common: decreased libido, impotence, menstrual cycle disorders; *Uncommon:* menorrhagia**;** Rare: galactorrhoea.

Respiratory system disorders - Common: dyspnoea, yawning; Very rare:

pulmonary eosinophilia.

Skin and subcutaneous tissue disorders -Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: erythema multiforme, Stevens Johnson syndrome.

Special senses - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation.

Adverse events from paediatric clinical trials

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

Withdrawal symptoms seen on discontinuation of venlafaxine treatment
Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

Special Notes:

In all premarketing depression trials with venlafaxine tablets, seizures were reported in 0.3% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in Efexor XL-treated patients in clinical trials for depression and GAD. No seizures occurred in placebo-treated patients in depression studies. Seizures were reported in 0.2% of placebo-treated patients in GAD studies (see section 4.4).

Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Efexor is usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.

Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy

Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

4.9 Overdose

Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia and seizures, hypotension, vertigo, serotonin syndrome and changes in level of consciousness have been reported in association with overdosage of venlafaxine usually when in combination with alcohol and/or other CNS drugs.

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

The haemodialysis clearance of venlafaxine and its main active metabolite, are low. Therefore, they are not considered dialysable.

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

Pharmacological Properties

5.1. Pharmacodynamic Properties

Efexor is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

The mechanism of Efexor's antidepressant action 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, are potent neuronal serotomn and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce B-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major

metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors in vitro. Pharmacologic activity at these receptors may be related to various side-effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular effects.

5.2 Pharmacokinetic Properties

Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the maj or active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak 0-desmethyl veniafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and nonmetabolised venlafaxine are excreted primarily through the kidneys.

5.3 Preclinical Safety Data

Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of in vitro and in vivo tests.

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 dose of 225mg/day

Pharmaceutical Particulars

6.1. List of Excipients

The active constituent is venlafaxine as hydrochloride. Other constituents are microcrystalline cellulose, lactose, sodium starch glycollate, magnesium stearate, yellow and brown iron oxide.

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

Three years

6.4. Special Precautions for Storage

Store in a dry place at room temperature (at or below 300C)

6.5. Nature and Contents of Container

PVC/aluminium foil blisters (pack size 28. 42, 56, 60 and 100)
White securitainers (pack size 28, 42, 56, 60 and 100)
High density polyethylene (HDPE) bottles (pack size 28, 42, 56, 60 and 100)
PVC/ACLAR/aluminium foil blisters (pack size 28, 42, 56, 60 and 100)
PVC/PVdC/aluminium foil blisters (pack size 28, 42, 56, 60 and 100)

6.6. Instruction for Use/Handling

None

7. MARKETING AUTHORISATION HOLDER

John Wyeth and Brother Limited
Huntercombe Lane South
Taplow
Maidenhead
Berks SL6 OPH
UK

8. MARKETING AUTHORISATION NUMBER(S)

50mg : 00011/0200

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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