**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0585/028/001**
Case No: 2036003

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Pliva Pharma Limited**

**Vision House**, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Venlafaxine 37.5 mg Tablets**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **01/08/2008** until **31/07/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Venlafaxine 37.5mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains venlafaxine hydrochloride, equivalent to 37.5mg of venlafaxine.
Excipients:
Venlafaxine 37.5mg Tablets contain 67.69mg of lactose
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

Light yellow, round, biconvex tablets, with marking VN 37 on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

**Moderate to severe major depressive disorder**
Venlafaxine Tablets are indicated for the treatment of moderate to severe 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 Venlafaxine Tablets are 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 Venlafaxine Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

**Adults:**
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Venlafaxine Tablets be taken with food.

If, after several weeks, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily).

There may be an increased risk of undesirable 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 by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300mg or more, treatment should be initiated under specialist supervision including shared care arrangement. The maximum recommended dose is 375 mg per day. 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.

**Patients with Renal or Hepatic Impairment:**

For patients with mild to moderate renal impairment (GFR 10-70 ml/minute) or mild to moderate hepatic impairment, the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients. For hemodialysis patients the dose should be reduced by 50% and venlafaxine should be taken after the hemodialysis.

Insufficient data are available to support the use of Venlafaxine Tablets 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 Venlafaxine Tablets in these patients (see sections 4.3 and 4.8).

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine Tablets for the individual patient. It is generally agreed that acute episodes of major
depression require several months or longer of sustained therapy. Venlafaxine Tablets have 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.

**Withdrawal symptoms seen on discontinuation of venlafaxine**
Abrupt discontinuation should be avoided (see section 4.4 and section 4.8). Following treatment with daily doses of venlafaxine greater than 75mg 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 Contraindications

- Known hypersensitivity to venlafaxine or to any of the excipients.
- Concomitant use of venlafaxine with monoamine oxidase inhibitors (MAOI) (see section 4.5).
- 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)
- Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder (see section 4.8).

## 4.4 Special warnings and precautions for use

**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.

**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). 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 section 4.2).

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

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

**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.

**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 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.

**Electrocardiogram findings:**
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.

**Blood pressure:**

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.

**Seizures:**
Seizures are a potential risk with antidepressant medicinal products-s, especially in overdose. Venlafaxine Tablets 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. Venlafaxine Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

**Drug abuse:**
Due to the possibility of drug abuse with CNS-active medicinal products, 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.

**Heart rate:**
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.

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

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

**Hyponatraemia:**
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.

**Mydriasis:**
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.

**Bleeding abnormalities:**
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.

**Serum cholesterol:**
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.

**Concomitant use with weight loss agents:**
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.

**Concomitant use with neuroleptics:**
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.

**Concomitant use with SSRIs:**
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.

**Use in children and adolescents under 18 years of age**
Venlafaxine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

**Diabetes**
For patients suffering from diabetes treatment with SSRI/SNRI can affect the glucose control. The insulin dose and/or peroral antidiabetics might have to be adjusted.

If rash, urticaria or other allergic reactions of any kind occur, treatment with venlafaxine must be discontinued.

Cautious dosing and regular checkups are called for in the following cases:
-Miction disturbances (e.g. prostate hypertrophy although the probability of the problems is very small, since venlafaxine has only a slight anticholinergic effect),
-Narrow angle glaucoma, increased intraocular pressure (the probability of the problems is small, since venlafaxine has only a slight anticholinergic effect),
-Low or high blood pressure,
-Cardiac diseases, like conduction disorders, angina pectoris and a recent myocardial infarction in connection of which normal precautions should also be performed. Caution should be taken in simultaneous administration of medicinal products.

**Lactose**
Venlafaxine Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products 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. Venlafaxine Tablets must not be used in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. At least 7 days should be allowed after stopping Venlafaxine Tablets before starting an MAOI (see section 4.3).

*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 medicinal products that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

The concomitant use of venlafaxine with products containing St. John's wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

*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 medicinal products, patients should be advised to avoid alcohol consumption while taking Venlafaxine Tablets.

*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 medicinal products 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 medicinal products: 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 Venlafaxine Tablets are 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 Venlafaxine Tablets are 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.

Medicinal products with a high protein-binding:
Since venlafaxine and ODV have low protein-binding (27 and 30 %, respectively) medicinal product interactions at this level are unlikely.

Alpha and beta sympathomimetics:
Alpha and beta sympathomimetics (adrenaline, noradrenaline, dopamine) in the event of a haemostatic procedure involving subcutaneous and gingival injections may cause ventricular heart rate disorder due to an increase of cardiac excitability.

Venlafaxine in association with alpha and beta sympathomimetics in the event of intravenous route may cause paroxysmal hypertension with possible heart rate disorders (inhibition of the entrance of the sympathomimetic medicinal product to the sympathetic fibre).

*Risperidone:*During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone and decreased CL/F (-38%) while the AUC of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-ripseridone) was not significantly changed.

## 4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse events of venlafaxine on pregnancy or health of the foetus. High concentrations of venlafaxine have been detected in amniotic fluid. Animal studies have shown reproductive toxicity (see section 5.3). . The potential risk for humans is unknown. Venlafaxine 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.

Lactation
Venlafaxine and its active metabolite are excreted in the breast milk. The effect on the infant is not clear. Therefore, a decision should be made whether to continue/discontinue breast-feeding or to continue/discontinue therapy with venlafaxine, taking into account the benefit of breast-feeding to the child and the benefit of venlafaxine therapy to the mother.

## 4.7 Effects on ability to drive and use machines

Venlafaxine has no or negligible influence on the 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 section 4.4.*
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 (≥ 1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000);very rare ( <1/10,000), not known (cannot be estimated from the available data):

Investigations
Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses *(see Section 4.4*), weight gain or loss; Uncommon: increased liver enzymes *(see below);* Rare: prolonged bleeding time; Very rare: prolactin increased.

Cardiac disorders (see section 4.4)
Common: palpitation; Uncommon: arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, ventricular fibrillation.

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).

Nervous system disorders
Very common: dizziness, headache, somnolence; Common: hypertonia, paraesthesia, tremor; Uncommon: altered taste, syncope, myoclonus; Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, neuroleptic malignant syndrome-like effects, seizures *(see below and Section 4.4),* serotonergic syndrome; Very rare: extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 ).

Eye disorders
Common: abnormal vision/ accommodation, mydriasis

Ear and labyrinth disorders
Common: tinnitus

Respiratory system disorders
Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

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

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

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; Not known: suicidal ideation and suicidal behaviour. Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

Metabolism and nutritional disorders
Uncommon: hyponatraemia including SIADH *(see Section 4.4)*.

Vascular disorders (*see Section 4.4*) - Common: hypertension, vasodilatation; Uncommon: hypotension/postural hypotension.

General disorders and adminstration site conditions
Very common: asthenia; Common: chills, pyrexia

Immune system disorders
Rare: anaphylaxis

Hepatobiliary disorders
Rare: hepatitis

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

Psychiatric disorders
Very common: insomnia, nervousness, somnolence; Common: abnormal dreams, agitation, anxiety, confusion; Uncommon: apathy, hallucinations; Rare: mania or hypomania *(see Section 4.4);* Very rare: delirium.

**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 and section 4.4).

**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 venlafaxine prolonged release tablet-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 Venlafaxine Tablets 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.

## 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 overdose of venlafaxine usually when in combination with alcohol and/or other CNS drugs.

Management of Overdose - An adequate airway, oxygenation and ventilation should be ensured. 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).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX16

Venlafaxine 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 venlafaxine’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 serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-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

Resorption
Venlafaxine is well absorbed and extensively metabolized in the liver. After a single administration of 25 – 150 mg venlafaxine as immediate-release tablets, peak plasma concentrations of venlafaxine and of the active main metabolite O-desmethylvenlafaxine are 37 – 163 and 61 – 325 ng/ml; they are attained within 2,1 – 2,4 and 4 – 4,6 h, respectively. After administration of 75 mg venlafaxine as extended-release capsules, peak plasma concentrations of 71 ± 40 and 122 ± 48 ng/ml respectively were reached within 5,5 and 9 hours. Plasma levels of venlafaxine and O-desmethylvenlafaxine are essentially dose-proportional. Following chronic administration no accumulation of venlafaxine or O-desmethylvenlafaxine was observed in test persons. Administration of venlafaxine as extended-release capsules with food has no effect on the absorption of venlafaxine, or on the subsequent formation of O-desmethylvenlafaxine.

Distribution
27 % of Venlafaxine and 30 % of O-desmethylvenlafaxine are bound to human plasma. After intravenous administration of venlafaxine, the volume of distribution is 4,4 ± 1,9 l/kg.

Metabolization
Venlafaxine undergoes extensive first -pass metabolism in the liver, primarily by the cytochrome P450 isoenzyme CYP2D6, to the main metabolite O-desmethylvenlafaxine. Although the relative activity of CYP2D6 can vary individually, no dose adjustment is necessary since venlafaxine and O-desmethylvenlafaxine have comparable pharmacological properties.
Metabolic elimination of venlafaxine is also catalysed by the cytochrome P450 isoenzyme CYP3A4. Venlafaxine inhibits CYP2D6 only weakly; inhibition of the isoenzymes CYP1A2, CYP2C9 and CYP3A4 could not be shown *in vitro*.
These findings were confirmed by *in vivo* drug interaction studies with the following active substances: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepin (CYP3A4), diazepam (CYP3A4 and CYP2C19) and tolbutamide (CYP2C9)

Elimination
Average half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and11 hours, respectively. After administration of 75 mg venlafaxine as extended release capsules, the apparent elimination half-life is 14,1 ±10,5 and 17,6 ± 6,5 hours, respectively. This is mainly determined by a delayed resorption and less by the elimination. Renal elimination of venlafaxine and its metabolites is the primary route of excretion. Approximately 87% of a venlafaxine dose is eliminated via urine within 48 hours as either unchanged venlafaxine, unconjugated O-desmethylvenlafaxine, conjugated ODV, or other minor inactive metabolites.

Age and gender
Age and gender have no clinically relevant impact on the pharmacological properties of venlafaxine and O-desmethylvenlafaxine.

Liver disease
In patients with compensated hepatic cirrhosis (moderate liver impairment), distribution of venlafaxine and O-desmethylvenlafaxine (ODV) was significantly changed. The lower metabolization of venlafaxine and the lower elimination of O-desmethylvenlafaxine resulted in increased plasma concentrations of venlafaxine and O-desmethylvenlafaxine. In a further study with oral and i.v. administration of venlafaxine in 21 subjects with liver impairment (mild [Child-Pugh A], n=11; moderate [Child Pugh B], n = 10) bioavailability and elimination half-life following oral administration of venlafaxine was nearly doubled compared with healthy subjects; clearance was reduced by more than half. Elimination half-life of ODV was prolonged by 40 %, clearance was comparable with healthy subjects. Considerable interindividual variability was observed.

Renal disease
In patients with moderate to severe renal impairment the total clearance of venlafaxine and O-desmethylvenlafaxine was reduced and the half-life was prolonged.

Bioavailability
Recovery of radioactively marked venlafaxine in the urine after a single oral administration of 50 mg was 92%, indicating an almost complete resorption. Due to an extensive first-pass metabolization to the active metabolite O-desmethylvenlafaxine, the absolute bioavailability of venlafaxine is reduced to 40-45%.

## 5.3 Preclinical safety data

Studies on chronic toxicity of venlafaxine focused on CNS effects. Venlafaxine and its main metabolite in humans showed no mutagenity in extensive tests. Long-term studies in rats and mice revealed no evidence of carcinogenesis. In studies on the reproductive toxicity in rats and rabbits no teratogenic, but embryotoxic effects were observed. Fetotoxicity manifested itself in rats as growth retardation in the lowest tested dosage (10 mg/kg) . Dosages above 10 mg/kg resulted in an increase in the perinatal and postnatal mortality which was probably caused by maternal toxicity.

In reproductive and fertility studies venlafaxine did not affect male and female fertility in rats given doses up to 8 times (mg/kg) and 2 times (mg/m2) respectively, the maximum recommended human daily dose. Male and female rats exposed to the main metabolite of venlafaxine O-desmethylvenlafaxine (ODV), showed reduced fertility. ODV exposition corresponded to 2-3 times the human dose of 225 mg. The relevance of these results for humans is unknown.
Preclinical Studies with venlafaxine suggest a partial blockage of cardiac sodium channels at micromolar concentrations. The connection with the occurrence of arrhythmia and ventricular fibrillation (see section 4.8 and 4.9) after overdose or inhibition of venlafaxine metabolization is unclear.

Long-term 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.
In studies on the reproductive toxicity in rats and rabbits no teratogenic, but embryotoxic effects were observed in rats. Decreases in the foetal weight, and increase in still birth and pup mortality were found at dose levels just above the maximum human daily dose.

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.

In vitro a partial blockage of cardiac sodium channels was observed at micromolar concentrations. The connection with the occurrence of arrhythmia and ventricular fibrillation after overdose or inhibition of venlafaxine metabolization is unclear.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Crospovidone Type A
Povidone K30
Lactose Monohydrate
Maize Starch
Copovidone K28
Iron oxide yellow (E172)
Silica, Colloidal Anhydrous
Magnesium Stearate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

18 months

## 6.4 Special precautions for storage

Store below 30°C.
Store in the original package.

## 6.5 Nature and contents of container

**PVC/PVdC//Al blister**
Pack sizes:
Venlafaxine 37.5mg Tablets: 20, 28, 50, 56, 100.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA0585/028/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: August 1st 2008

## 10 DATE OF REVISION OF THE TEXT