IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0749/122/002
Case No: 2081729

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

Transferred from PA1017/013/002.

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

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

Venixaf XL 150 mg Prolong-release Capsules

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 **30/04/2010** until **30/03/2015**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Venixaf XL 150 mg Prolonged-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150mg of venlafaxine (as 169.71 mg venlafaxine hydrochloride).

Excipient:
Each capsule contains no more than 186.76 mg of sucrose as Sugar spheres.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

Hard gelatin capsule with natural transparent cap and body. Each capsule contains white or whitish pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- treatment of major depressive episodes
- prevention of recurrence of major depressive episodes

4.2 Posology and method of administration

Major depressive episodes
The recommended starting dose of venlafaxine is 75 mg/day in two or three divided doses taken with food. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly on a case-by-case basis. Longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during the current episode.

Antidepressive medicinal products should continue for at least six months following remission.

Use in elderly patients
No specific dose adjustments of venlafaxine are considered necessary based on patient age alone.
However, caution should be exercised in treating the elderly (e.g., due to the possibility of renal impairment, the potential for changes in neurotransmitter sensitivity and affinity occurring with aging). The lowest effective dose should always be used, and patients should be carefully monitored when an increase in the dose is required.

Use in children and adolescents under the age of 18 years
Venlafaxine is not recommended for use in children and adolescents.
Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

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

Use in patients with hepatic impairment
In patients with mild and moderate hepatic impairment, in general a 50% dose reduction should be considered. However, due to inter-individual variability in clearance, individualisation of dosage may be desirable.

There are limited data in patients with severe hepatic impairment. Caution is advised, and a dose reduction by more than 50% should be considered. The potential benefit should be weighed against the risk in the treatment of patients with severe hepatic impairment.

Use in patients with renal impairment
Although no change in dosage is necessary for patients with glomerular filtration rate (GFR) between 30-70 ml/minute, caution is advised. For patients that require haemodialysis and in patients with severe renal impairment (GFR < 30 ml/min), the dose should be reduced by 50%. Because of inter-individual variability in clearance in these patients, individualisation of dosage may be desirable.

Withdrawal symptoms seen on discontinuation of venlafaxine
Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). 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.

For oral use.

It is recommended that venlafaxine tablets be taken with food, at approximately the same time each day.

Patients treated with venlafaxine immediate-release tablets may be switched to Venlafaxine prolonged-release capsules at the nearest equivalent daily dosage. For example, Venlafaxine immediate-release tablets 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

4.3 Contraindications

- Hypersensitivity to venlafaxine or to any of the excipients
- Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI.

Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see sections 4.4 and 4.5).

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.

Use in children and adolescents under 18 years of age
Efexor 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.

Serotonin syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents, such as MAOinhibitors, that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

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

Blood pressure
Dose-related increases in blood pressure have been commonly reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in postmarketing experience. All patients should be carefully screened for high blood pressure and preexisting hypertension should be controlled before initation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

Heart rate
Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

Cardiac disease and risk of arrhythmia
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.

In postmarketing experience, fatal cardiac arrhythmias have been reported with the use of venlafaxine, especially in overdose. The balance of risks and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia.

Convulsions
Convulsions may occur with venlafaxine therapy. As with all antidepressants, venlafaxine should be introduced with caution in patients with a history of convulsions, and concerned patients should be closely monitored. Treatment should be discontinued in any patient who develops seizures.

Hyponatraemia
Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported 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.

Abnormal bleeding
Medicinal products that inhibit serotonin uptake may lead to reduced platelet function. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

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

Co-administration 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.

Mania/hypomania
Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with other antidepressants, venlafaxine should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression
Aggression may occur in a small number of patients who have received antidepressants, including venlafaxine. This has been reported under initiation, dose changes and discontinuation of treatment. As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

Discontinuation of 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 (tapering and post-tapering) occurred in approximately 35% of patients treated with venlafaxine and 17% of patients taking placebo.

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), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported 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).

Akathisia/psychomotor restlessness
The use of venlafaxine has been associated with the development of 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.

Dry mouth
Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

Sucrose intolerance
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)
Irreversible non-selective MAOIs
Venlafaxine must not be used in combination with irreversible non-selective MAOIs. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI (see sections 4.3 and 4.4).

Reversible, selective MAO-A inhibitor (moclobemide)
Due to the risk of serotonin syndrome, the combination of venlafaxine with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of Venlafaxine treatment. It is recommended that venlafaxine should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

Reversible, non-selective MAOI (linezolid)
The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with venlafaxine (see section 4.4).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or have recently had venlafaxine therapy discontinued prior toinitiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Serotonin syndrome
As with other serotonergic agents, serotonin syndrome may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [Hypericum perforatum]), with medicinal agents which impair metabolism of serotonin (including MAOIs), or with serotonin precursors (such as tryptophan supplements).

If concomitant treatment of venlafaxine with an SSRI, an SNRI or a serotonin 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 (see section 4.4).

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

Ethanol
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 venlafaxine.

Lithium: Venlafaxine had no effect on the pharmacokinetics of lithium.

Effect of other medicinal products on venlafaxine
Ketoconazole (CYP3A4 inhibitor)
A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine (70% and 21% in CYP2D6 PM and EM subjects, respectively) and O-desmethylvenlafaxine (33% and 23% in CYP2D6 PM and EM subjects, respectively) following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and O-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly.

Effect of venlafaxine on other medicinal products

Lithium
Serotonin syndrome may occur with the concomitant use of venlafaxine and lithium (see Serotonin syndrome).

Diazepam
Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or O-desmethylvenlafaxine. It is unknown whether a pharmacokinetic and/or pharmacodynamic interaction with other benzodiazepines exists.

Imipramine
Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2.5 to 4.5-fold when venlafaxine 75 mg to 150 mg daily was administered. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of venlafaxine and imipramine.

Haloperidol
A pharmacokinetic study with haloperidol has shown a 42% decrease in total oral clearance, a 70% increase in AUC, an 88% increase in Cmax, but no change in half-life for haloperidol. This should be taken into account in patients treated with haloperidol and venlafaxine concomitantly. The clinical significance of this interaction is unknown.

Risperidone
Venlafaxine increased the risperidone AUC by 50%, but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

Metoprolol
Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicinal products resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of venlafaxine and metoprolol.

Indinavir
A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in Cmax for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

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.

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. Neonates exposed to venlafaxine late in the third trimester have developed complications requiring respiratory support or prolonged hospitalisation.

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

The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency.

Frequencies are defined 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), not known (cannot be estimated from the available data).

Body System	Very Common	Common	Uncommon	Rare	Not Known
Haematological / Lymphatic			Ecchymosis, Gastrointestinal haemorrhage		Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopaenia , Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopaenia)
Metabolic/ Nutritional		Serum cholesterol increased, Weight loss	Weight gain		Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased
Nervous	Dry mouth (10.0%), Headache (30.3%)*	Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation	Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance	Akathisia/ Psychomotor restlessness, Convulsion, Manic reaction	Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinaesia), Tardive dyskinaesia, Suicidal ideation and behaviours**

Body System	Very Common	Common	Uncommon	Rare	Not Known
Special Senses		Abnormality of accommodation, Mydriasis, Visual disturbance,	Altered taste sensation, Tinnitus		Angle-closure glaucoma
Cardiovascular		Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations	Postural hypotension, Syncope, Tachycardia		Hypotension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)
Respiratory		Yawning			Pulmonary eosinophilia
Digestive	Nausea (20.0%)	Appetite decreased (anorexia), Constipation, Vomiting	Bruxism, Diarrhoea		Pancreatitis
Skin	Sweating (including night sweats) [12.2%]		Rash, Alopecia		Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria
Musculoskeletal					Rhabdomyolysis
Urogenital		Abnormal ejaculation/orgas m (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria	Abnormal orgasm (females), Urinary retention		
Body as a Whole		Asthenia (fatigue), Chills	Photosensitivity reaction		Anaphylaxis

* In pooled clinical trials, the incidence of headache was 30.3% with venlafaxine versus 31.3% with placebo.

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

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraethesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache and flu syndrome are the most commonly reported reactions. 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 sections 4.2 and 4.4).

Paediatric patients
In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).
In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

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

4.9 Overdose

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

There have been some reports of fatalities in patients taking overdoses of Venlafaxine, predominantly 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Psychoanaleptics – Other Antidepressants
ATC code: N06AX 16
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, ODV, are potent inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Studies in animals show that tricyclic antidepressants may reduce ß-adrenergic responsiveness following chronic administration. In contrast, venlafaxine and ODV reduce ß-adrenergic responsiveness after both acute (single dose) and chronic administration.

Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake.

Venlafaxine has virtually no affinity for rat brain muscarinic cholinergic, H_1-histaminergic or a_1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular side effects.

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. 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.

5.2 Pharmacokinetic properties

At least 92% of a single oral dose of venlafaxine is absorbed. After administration of venlafaxine, the peak plasma concentrations of venlafaxine and ODV are attained within 6.0 ± 1.5 and 8.8 ± 2.2 hours, respectively. The rate of absorption of venlafaxine from the venlafaxine capsules is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of venlafaxine capsules (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 daily doses of venlafaxine were administered as either the immediate release tablet, or the extended release capsule, 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 venlafaxine capsule. Therefore, the venlafaxine capsule provides a slower rate of absorption, but the same extent of absorption (i.e. AUC), as the Venlafaxine immediate release tablet.

Venlafaxine undergoes extensive first-pass metabolism in the liver, primarily by CYP2D6, to the major metabolite ODV. Venlafaxine is also metabolised to N-desmethylvenlafaxine, catalysed by CYP3A3/4, and to other minor metabolites.

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine, unconjugated ODV, conjugated ODV, or other minor metabolites.

The half lives of venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) are increased in patients with renal and hepatic impairment.

A clinical study demonstrated that in hepatically impaired patients the mean plasma half-life of venlafaxine is approximately doubled (see Section 4.2).

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

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.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times on a mg/m^2 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 ODV exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres 20 (containing sucrose and maize starch)
Stearic acid
Ethylcellulose
Talc

Capsule
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store below 30ºC. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al/PVDC/-PVC/PVDC blisters - pack sizes 14, 28 30
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B V
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/122/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st March 2010

10 DATE OF REVISION OF THE TEXT

April 2010