IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1380/063/003
Case No: 2057893

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Velexor 50 mg film-coated 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 **15/05/2009** until **14/05/2014**.

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

Velexor 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Velexor 50 mg film-coated tablets: One tablet contains 56.56 mg venlafaxine hydrochloride, equivalent to 50 mg venlafaxine. Contains lactose monohydrate equivalent to lactose 34.84 mg and sunset yellow FCF lake (E110) 0.06 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Vexelor 50 mg are orange, round and biconvex film-coated tablets 8 mm in diameter and marked with V3.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

4.2 Posology and method of administration

Major depressive episodes
The recommended starting dose of immediate-release 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 occuring 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 immediate-release 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.

For doses not realisable/practicable with this strength, other strengths of medicinal products containing venlafaxine are available.

4.3 Contraindications

Hypersensitivity to the active substance 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
Velexor 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 MAO-inhibitors, 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 pre-existing 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.

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

Colourant
Sunset yellow FCF lake may cause allergic reactions.

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 to initiation 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 and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

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 $C_{max,}$ 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 C_{max} 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

Pregnancy
There are no adequate data from the use of venlafaxine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk.

As with other serotonin reuptake inhibitors (SSRIs/SNRIs), discontinuation symptoms may occur in the newborns if venlafaxine is used until or shortly before birth. Some newborns exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can arise immediately upon delivery.

The following symptoms may be observed in neonates if the mother has used an SSRI/SNRI late in pregnancy: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping. These symptoms may be due to either serotonergic effects or exposure symptoms. In the majority of cases, these complications are observed immediately or within 24 hours after partus.

Lactation
Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with Velexor should be made, taking into account the benefit of breast-feeding to the child and the benefit of Velexor therapy to the woman.

4.7 Effects on ability to drive and use machines

Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine 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), very rare (1<10,000), not known (cannot be estimated from the available data).

Body System	Very Common	Common	Uncommon	Rare	Not known
Investigations		Serum cholesterol increased			Prolactin increased

Cardiac disorders		Palpitations	Tachycardia		QT prolongation, ventricular fibrillation, ventricular tachycardia (including torsade de pointes)
Blood and lymphatic system disorders			Ecchymosis, gastrointestinal haemorrhage		Mucous membrane bleeding, prolonged bleeding time, thrombo-cytopaenia, blood dyscrasias, (including agranulo-cytosis, aplastic anaemia, neutropaenia and pancytopaenia)
Nervous system disorders	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, altered taste sensation,	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**
Eye disorders		Abnormality of accommod-ation, mydriasis, visual disturbance			Angle-closure glaucoma
Ear and labyrinth disorders			Tinnitus		

Respiratory, thoracic and mediastinal disorders		Yawning			Pulmonary eosinophilia
Gastro-intestinal disorders	Nausea (20.0%)	Appetite decreased (anorexia), constipation, vomiting	Bruxism, diarrhoea		Pancreatitis
Renal and urinary disorders		urination impaired (mostly hesitancy), pollakiuria	Urinary retention		
Skin and subcutaneous tissue disorders	Sweating (including night sweats) [12.2%]		Rash, alopecia		Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, pruritus, urticaria
Musculo-skeletal and connective tissue disorders					Rhabdo-myolysis
Metabolism and nutrition disorders		Weight loss	Weight gain		Hyponatraemia syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Vascular disorders		Hypertension, vasodilatation (mostly hot flashes/-flushes)	Postural hypotension, syncope		Hypotension
General disorders and administration site conditions		Asthenia (fatigue), chills	Photo-sensitivity reaction		Anaphylaxis
Hepatobiliary disorders					Abnormal liver function tests, hepatitis

Reproductive system and breast disorders		Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia)			
Psychiatric disorders		Abnormal ejaculation/orgasm (males), anorgasmia, erectile dysfunction (impotence)	Abnormal orgasm (females)		

*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

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other reported events include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear.

Prescriptions for venlafaxine should be written for the smallest quantity of the medicinal product consistent with good patient management in order to reduce the risk of overdose.

Recommended treatment
General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored. When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit absorption of the active substance. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants - ATC code: NO6A X16.

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 (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-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 and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H_1-histaminergic or α1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicinal products, 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 or benzodiazepine sensitive receptors.

Major depressive episodes
The efficacy of venlafaxine immediate-release as a treatment for major depressive episodes was demonstrated in five randomised, double-blind, placebo-controlled, short-term trials ranging from 4 to 6 weeks duration, for doses up to 375 mg/day. The efficacy of venlafaxine prolonged-release as a treatment for major depressive episodes was established in two placebo-controlled, short-term studies for 8 and 12 weeks duration, which included a dose range of 75 to 225 mg/day.

In one longer-term study, adult outpatients who had responded during an 8-week open trial on venlafaxine prolonged-release (75, 150, or 225 mg) were randomised to continuation of their same venlafaxine prolonged-release dose or to placebo, for up to 26 weeks of observation for relapse.

In a second longer-term study, the efficacy of venlafaxine in prevention of recurrent depressive episodes for a 12-month period was established in a placebo-controlled double-blind clinical trial in adult outpatients with recurrent major depressive episodes who had responded to venlafaxine treatment (100 to 200 mg/day, on a b.i.d. schedule) on the last episode of depression.

5.2 Pharmacokinetic properties

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Mean ± SD plasma half-lives of venlafaxine and ODV are 5±2 hours and 11±2 hours, respectively. Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Absorption
At least 92 % of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40 % to 45 % due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet. Food does not affect the bioavailability of venlafaxine and ODV.

Distribution
Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27 % and 30 %, respectively). The volume of distribution for venlafaxine at steady-state is 4.4±1.6 L/kg following intravenous administration.

Metabolism
Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. *In vitro* and *in vivo* studies indicate that venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9, or CYP3A4.

Elimination
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 (5 %), unconjugated ODV (29 %), conjugated ODV (26 %), or other minor inactive metabolites (27 %). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1.3±0.6 L/h/kg and 0.4±0.2 L/h/kg, respectively.

Special populations

Age and gender
Subject age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.

CYP2D6 extensive/poor metabolisers
Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

Patients with hepatic impairment
In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were prolonged compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

Patients with renal impairment
In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance reduced by about 57% compared to normal subjects, while ODV elimination half-life was prolonged by about 142% and clearance reduced by about 56%. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

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.

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown.

These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.

Reduced fertility was observed in a study in which both male and female rats were exposed to ODV. This exposure was approximately 1 to 2 times that of a human venlafaxine dose of 375 mg/day. The human relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Povidone (K30)
Magnesium stearate

Tablet coat:
Opadry 03B23319 consisting of
hypromellose
titanium dioxide (E 171)
macrogol 400
Sunset yellow FCF lake (E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Al blister

Pack sizes: 20, 50 or 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.,
Reykjavikurvegi 76-78,
220 Hafnarfjörður,
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/63/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th May 2009

10 DATE OF REVISION OF THE TEXT