Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Venlatev 150 mg hard prolonged-release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard prolonged-release capsule contains venlafaxine hydrochloride, equivalent to 150 mg of venlafaxine.

Venlatev150 mg:
Each hard prolonged-release capsule contains 139.7 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard prolonged-release capsule

Venlatev150 mg:
Capsules of hard gelatin, with an opaque brown cap and opaque brown body filled with white to beige micro granules. The capsules are marked with black ink on the cap with "VNL" and the number "150" on the body. The capsule is approximately 24 mm x 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

Treatment of generalised anxiety disorder.

Treatment of social anxiety disorder.

Treatment of panic disorder, with or without agoraphobia.

4.2 Posology and method of administration

Posology

Major depressive episodes
The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dose 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 current episode.

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

Generalised anxiety disorder

The recommended starting dose for prolonged-release venlafaxine is 75 mg given once daily. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 225 mg/day. Dose increases can be made at intervals of 2 weeks or more.

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.

Social anxiety disorder

The recommended dose for prolonged-release venlafaxine is 75 mg given once daily. There is no evidence that higher doses confer any additional benefit.

However, in individual patients not responding to the initial 75 mg/day, increases up to a maximum dose of 225 mg/day may be considered. Dose increases can be made at intervals of 2 weeks or more.
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.

Panic disorder

It is recommended that a dose of 37.5 mg/day of prolonged-release venlafaxine be used for 7 days. Dose should then be increased to 75 mg/day. Patients not responding to the 75 mg/day dose may benefit from dose increases up to a maximum of 225 mg/day. Dose increases can be made at intervals of 2 weeks or more.

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.

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). However, the time period required for tapering and the amount of dose reduction may depend on the dose, duration of therapy and the individual patient. In some patients, discontinuation may need to occur very gradually over periods of months or longer. 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.

Special populations

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.

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 dose 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.

Patients with renal impairment

Although no change in dose 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.

Paediatric population

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.

Method of administration

For oral use.

It is recommended that venlafaxine prolonged-release capsules be taken with food, at approximately the same time each day. The capsules must be swallowed whole with the liquid and not divided, crushed, chewed, or dissolved.

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

Venlafaxine prolonged-release capsules contain spheroids that slowly release the drug into the digestive tract. The insoluble portion of these spheroids is excreted and may be visible in the faeces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Overdose

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects (section 4.5). Overdose with venlafaxine has been reported predominantly in combination with alcohol and/or other medicinal products, including cases with fatal outcome (section 4.9).

Prescriptions for venlafaxine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose (see 4.9).

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 antidepressants 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.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potenially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other substances that affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, St. John's Wort (*Hypericum perforatum*), opiods (e.g. buprenorphine, fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), medicinal products that affect the metabolism of serotonin (e.g. MAOIs such as methylene blue),serotonin precursors (such as trytophan supplements), or antipsychotics or other dopamine antagonists (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). Serotonin syndrome in its most severe form, can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

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

The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

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, cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia, and fatal cardiac arrhythmias have been reported with the use of venlafaxine, especially in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia or QTc prolongation (see section 5.1).

Convulsions

Convulsions may occur with venlafaxine therapy. 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. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis and petechiae to gastrointestinal and life-threatening haemorrhages. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). The risk of haemorrhage may be increased in patients taking venlafaxine. 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 medicinal products

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

Mania/hypomania

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. 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.
Venlafaxine should be used cautiously in patients with a history of aggression.

Discontinuation of treatment

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe. Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including during discontinuation. Therefore, patients should be closely monitored when the dose is reduced or during discontinuation (see above in section 4.4 "Suicide/Suicidal thoughts or clinical worsening" and "Aggression"). Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse effects seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 31% 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, headache, visual impairment and hypertension 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). In some patients, discontinuation could take months or longer.

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.

Diabetes

In patients with diabetes, treatment with an SSRI or venlafaxine may alter glycaemic control. Insulin and/or oral antidiabetic dose may need to be adjusted.

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.
Venlatev
Excipient warning:
Sucrose:
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Paediatric population

Venlatevshould 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 (predominantely aggression, oppositional behavior 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.

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, a potentially life-threatening condition, may occur with venlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, St. John's Wort *[Hypericum perforatum],* opioids (e.g. buprenorphine,fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine)), with medicinal agents that affect the metabolism of serotonin (e.g. MAOIs such as methylene blue), serotonin precursors (e.g. tryptophan dietary supplements) or antipsychotics or other dopamine antagonists (see sections 4.3 and 4.4).

If concomitant treatment with venlafaxine and 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

Patients should be advised not to use alcohol, considering its CNS-effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with venlafaxine including CNS depressant effects.

Medicinal products that prolong the QT Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) is increased with concomitant use of other medicinal products which prolong the QTc interval. Co-administration of such medicinal products should be avoided (see section 4.4).

Relevant classes include:

- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)

- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines
- some quinolone antibiotics (e.g. moxifloxacin)

The above list is not exhaustive and other individual medicinal products known to significantly increase QT interval should be avoided.

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.

Drugs Metabolized by Cytochrome P450 Isoenzymes

In vivo studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) or CYP2C19 (diazepam) *in vivo*.

Oral contraceptives

In post-marketing experience unintended pregnancies have been reported in subjects taking oral contraceptives while on venlafaxine. There is no clear evidence these pregnancies were a result of drug interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

4.6 Fertility, 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.

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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with venlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4 and 4.8).

Breast-feeding

Venlafaxine and its active metabolite, O-desmethyl-venlafaxine, are excreted in breast milk. There have been postmarketing reports of breast-fed infants who experienced crying, irritability, and abnormal sleep patterns. Symptoms consistent with venlafaxine discontinuation have also been reported after stopping breast-feeding. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with Venlatev should be made, taking into account the benefit of breast-feeding to the child and the benefit of Venlatev therapy to the woman.

Fertility

Reduced fertility was observed in a study in which both male and female rats were exposed to O-desmethyl-venlafaxine. The human relevance of this finding is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Venlatev 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

Summary of the safety profile
Adverse reactions reported as very common (>1/10) in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Tabulated list of adverse reactions
Adverse reactions are listed below by system organ class, frequency category and decreasing order of medical seriousness within each frequency category.

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	Very Rare	Not Known
Blood and lymphatic system disorders				Agranulocytosis*, Aplastic anaemia*, Pancytopaenia*, Neutropaenia*	Thrombocytopaenia*	
Immune system disorders				Anaphylactic reaction*		
Endocrine disorders				Inappropriate antidiuretic hormone secretion*	Blood prolactin increased*	
Metabolism and		Decreased		Hyponatraemia*		

nutrition disorders		appetite				
Psychiatric disorders	Insomnia	Confusional state*, Depersonalization*, Abnormal dreams, Nervousness, Libido decreased, Agitation*, Anorgasmia	Mania, Hypomania, Hallucination, Derealization, Abnormal orgasm, Bruxism*, Apathy	Delirium*		Suicidal ideation and suicidal behaviours[a] Aggression[b]
Nervous system disorders	Headache[c], Dizziness, Sedation	Akathisia*, Tremor, Paraesthesia, Dysgeusia	Syncope, Myoclonus, Balance disorder*, Coordination abnormal*, Dyskinaesia*	Neuroleptic Malignant Syndrome (NMS)*, Serotonin syndrome*, Convulsion, Dystonia*	Tardive dyskinaesia*	
Eye disorders		Visual impairment, Accommodation disorder, including vision blurred, Mydriasis		Angle-closure glaucoma*		
Ear and labyrinth disorders		Tinnitus*				Vertigo
Cardiac disorders		Tachycardia, Palpitations*		Torsade de pointes*, Ventricular tachycardia*, Ventricular fibrillation, Electrocardiogram QT prolonged*		Stress cardiomyopathy (takotsubo cardiomyopathy)*
Vascular disorders		Hypertension, Hot flush	Orthostatic hypotension, Hypotension*			
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, Yawning		Interstitial lung disease*, Pulmonary eosinophilia*		
Gastrointestinal disorders	Nausea, Dry mouth, Constipation	Diarrhoea*, Vomiting	Gastrointestinal haemorrhage*	Pancreatitis*		
Hepatobiliary disorders			Liver function test abnormal*	Hepatitis*		
Skin and subcutaneous tissue disorders	Hyperhidrosis* (including night sweats)*	Rash, Pruritus*	Urticaria*, Alopecia*, Ecchymosis, Angioedema*, Photosensitivity reaction	Stevens-Johnson syndrome*, Toxic epidermal necrolysis*, Erythema multiforme*		
Musculoskeletal and connective		Hypertonia		Rhabdomyolysis*		

tissue disorders						
Renal and urinary disorders		Urinary hesitation, Urinary retention, Pollakiuria*	Urinary incontinence*			
Reproductive system and breast disorders		Menorrhagia*, Metrorrhagia*, Erectile dysfunction[b], Ejaculation disorder[b]				Postpartum haemorrhage[d*]
General disorders and administration site conditions		Fatigue, Asthenia, Chills*			Mucosal haemorrhage*	
Investigations		Weight decreased, Weight increased, Blood cholesterol increased			Bleeding time prolonged*	

* ADR identified postmarketing

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

[b] See section 4.4

[c] In pooled clinical trials, the incidence of headache with venlafaxine and placebo were similar.

[d] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

Discontinuation of treatment

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, vertigo, headache flu syndrome, visual impairment and hypertension 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). However, some patients have experienced severe aggression and suicidal ideation during dose reduction or discontinuation (see sections 4.2 and 4.4).

Paediatric population

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms
In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products, *including cases with fatal outcome*. 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 [see section 5.1]), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia, vertigo, and deaths. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

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

Recommended treatment

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with [*e.g. national poison information center, poisoning specialist, to be adapted nationally*] is recommended.

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: Nervous system; psychoanaleptics; antidepressants; Other antidepressants
ATC code: N06A X16

Mechanism of action

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, H1-histaminergic or α_1-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.

Clinical efficacy and safety

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 twice daily schedule) on the last episode of depression.

Generalised anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for generalised anxiety disorder (GAD) was established in two 8-week, placebo-controlled, fixed-dose studies (75 to 225 mg/day), one 6-month, placebo-controlled, fixed-dose study (75 to 225 mg/day), and one 6-month, placebo-controlled, flexible-dose study (37.5, 75, and 150 mg/day) in adult outpatients.

While there was also evidence for superiority over placebo for the 37.5 mg/day dose, this dose was not as consistently effective as the higher doses.

Social anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for social anxiety disorder was established in four double-blind, parallel-group, 12-week, multi-centre, placebo-controlled, flexible-dose studies and one double-blind, parallel-group, 6-month, placebo-controlled, fixed/flexible-dose study in adult outpatients. Patients received doses in a range of 75 to 225 mg/day. There was no evidence for any greater effectiveness of the 150 to 225 mg/day group compared to the 75 mg/day group in the 6-month study.

Panic disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for panic disorder was established in two double-blind, 12-week, multi-centre, placebo-controlled studies in adult outpatients with panic disorder, with or without agoraphobia. The initial dose in panic disorder studies was 37.5 mg/day for 7 days. Patients then received fixed doses of 75 or 150 mg/day in one study and 75 or 225 mg/day in the other study.

Efficacy was also established in one long-term double-blind, placebo-controlled, parallel-group study of the long-term safety, efficacy, and prevention of relapse in adult outpatients who responded to open-label treatment. Patients continued to receive the same dose of venlafaxine prolonged-release that they had taken at the end of the open-label phase (75, 150, or 225 mg).

Cardiac electrophysiology
In a dedicated thorough QTc study in healthy subjects, venlafaxine did not prolong the QT interval to any clinically relevant extent at a supra-therapeutic dose of 450 mg/day (given as 225 mg twice daily).
However, postmarketing cases of QTc prolongation/TdP and ventricular arrhythmia have been reported, especially in overdose or in patients with other risk factors for QTc prolongation/TdP (see sections 4.4, 4.8 and 4.9).

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.

Biotransformation

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.

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).

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 %. Dose 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

Capsule contents:
Sugar spheres (sucrose + maize starch)
Hypromellose
Ethylcellulose
Talc

Capsule shell:
Yellow Iron Oxide (E 172)
Titanium dioxide (E 171)
Gelatin
Red Iron Oxide (E 172)

Printing ink:
Shellac
Propylene glycol (E 1520)
Strong amonia solution
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Alu//PVC/PVDC blisters
Pack size: 10, 14, 20, 28, 30, 50, 98, 100 hard prolonged release capsules

Alu//PVC/PVDC perforated unit dose blisters
Pack size: 100 x 1 hard prolonged release capsules

HDPE bottles with PP screw cap
37.5 mg prolonged release capsules
Pack size: 150 hard prolonged release capsules

75 mg prolonged release capsules
150 mg prolonged release capsules
Pack size: 30, 150 hard prolonged release capsules

Not all pack sizes may be marketed.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Alu//PVC/PVDC blisters
Pack size: 10, 14, 20, 28, 30, 50, 98, 100 hard prolonged release capsules

Alu//PVC/PVDC perforated unit dose blisters
Pack size: 100 x 1 hard prolonged release capsules

HDPE bottles with PP screw cap
37.5 mg prolonged release capsules
Pack size: 150 hard prolonged release capsules

75 mg prolonged release capsules
150 mg prolonged release capsules

Pack size: 30, 150 hard prolonged release capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/099/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th April 2021
Date of last renewal: 4th March 2026

10 DATE OF REVISION OF THE TEXT

September 2025