For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Prolonged-Rel. venlafaxine CAP

1. Generic Name

Venlafaxine

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:
Venlafaxine Hydrochloride I.P.
Equivalent to venlafaxine 75 mg
(In the form of extended-release pellets)
Approved colours used in hard gelatin capsule shells

Other excipients are Talc, Ethyl cellulose, hydroxy propyl methyl cellulose, methanol, methelyene chloride, ethyl cellulose.

3. Dosage form and strength

Dosage form: Hard gelatin capsules
Strength: 75mg

4. Clinical particulars

4.1 Therapeutic indication

Venlafaxine indicated in the treatment of Major depression.

4.2 Posology and method of administration

Major depressive episodes

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

No specific dose adjustments of venlafaxine are considered necessary based on patient age alone. However, caution should be exercised in treating older people (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.

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 30-70ml/minute, caution is advised. For patients that require haemodialysis and in patients with severe renal impairment (GFR < 30ml/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 prolonged-release capsules be taken with food, at approximately the same time each day. Capsules must be swallowed whole with fluid 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 dosage. For example, venlafaxine immediate-release tablets 37.5mg twice daily may be switched to venlafaxine prolonged-release capsules 75mg once daily. Individual dosage adjustments may be necessary.

Venlafaxine prolonged-release capsules contain spheroids, which release the active substance slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in faeces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed.

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

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

Prolonged-Rel. venlafaxine CAP 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 that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St. John's Wort [Hypericum perforatum], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone

and pentazocine), with medicinal agents that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

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

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. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to gastrointestinal and life threatening haemorrhages. 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 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 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).

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/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.

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 a SSRI or venlafaxine may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

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.

4.5 Drugs interactions

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 nonselective 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

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, amphetamines, lithium, sibutramine, St. John's Wort [*Hypericum perforatum*], fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicinal agents that impair metabolism of serotonin (such as MAOIs e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.4).

If concomitant treatment of venlafaxine with a 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.

Drugs 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 pharmacodynamics 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 Use in special populations

Pregnancy

There are no adequate data from the use of venlafaxine in pregnant women. Studies in animals have shown reproductive toxicity. Venlafaxine must only be administered to pregnant women if the expected benefits outweigh any possible risk.

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 Prolonged-Rel. venlafaxine CAP taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

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 a 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.

Breast-feeding

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in breast milk. There have been post-marketing reports of breast-fed infants who experienced crying, irritability and abnormal sleep patterns. Symptoms consistent with venlafaxine drug 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 venlafaxine should be made, taking into account the benefit of breast-feeding to the child and the benefit of venlafaxine therapy to the woman.

Fertility

Reduced fertility was observed in a study in which both male and female rats were exposed to O-desmethylvenlafaxine. The human relevance of this finding is unknown

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 reported clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

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*, Pancytopenia*, Neutropaenia*	Thrombocytopenia*	
Immune system disorders				Anaphylactic reaction*		
Endocrine disorders				Inappropriate antidiuretic hormone secretion*	Blood prolactin increased*	
Metabolism and nutrition disorders		Decreased appetite		Hyponatraemia*		
Psychiatric disorders	Insomnia	Confusional state*, Depersonalization*, Abnormal dreams, Nervousnes	Mania, Hypomania, Hallucination, Derealization, Abnormal orgasm,	Delirium*		Suicidal ideation and suicidal behaviours[a],

Body System	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
		s, Libido decreased, Agitation*, Anorgasmia,	Bruxism*, Apathy			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*		
Vascular disorders		Hypertension, Hot flush	Orthostatic hypotension, Hypotension*			
Respiratory, thoracic and		Dyspnoea*, Yawning		Interstitial lung disease*,		

Body System	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
mediastinal disorders				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 tissue disorders		Hypertonia		Rhabdomyolysis*		
Renal and urinary disorders		Urinary hesitation, Urinary retention, Pollakiuria*	Urinary incontinence*			
Reproductive system and breast disorders		Menorrhagia*, Metrorrhagia*, Erectile dysfunction, Ejaculation disorder				
General disorders and administrati		Fatigue, Asthenia, Chills*			Mucosal haemorrhage*	

Body System	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
on site conditions						
Investigations		Weight decreased, Weight increased, Blood cholesterol increased			Bleeding time prolonged*	

*ADR identified post-marketing

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.

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 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.

In reported 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 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 any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

In post marketing 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 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 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.

5.2 Pharmacodynamics 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, H1-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.

5.3 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±1.6L/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±0.6L/h/kg and 0.4±0.2L/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

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

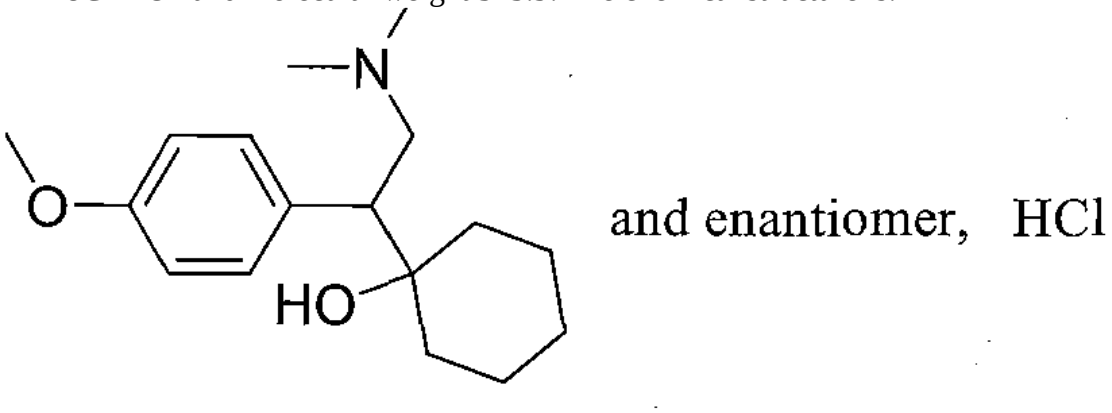
Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of *in vitro* and *in vivo* tests.

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 30mg/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 375mg/day. The human relevance of this finding is unknown.

7. Description

Venlafaxine Hydrochloride is 1-[(lRS)-2-(dimethy}.amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride. Having molecular formula C17H28CLNO2 and molecular weight 313.9. The chemical structure is:



White to off white Colour. Other excipients are Talc, Ethyl cellulose, Hydroxy propyl methyl cellulose, methanol, methelyene chloride, ethyl cellulose.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Prolonged-Rel.venlafaxine CAP Available in blister strip of 10 tablets.

8.4 Storage and handing instructions

Store in dry place at a temperature not exceeding 30 º C.

9. Patient Counselling Information

Prolonged-Rel.venlafaxine CAP

(Venlafaxine)

Six important things you need to know about prolonged-rel. Venlafaxine cap

■ Prolonged-Rel. venlafaxine CAP treats depression. Like all medicines it can also have unwanted effects. It is important that you and your doctor discuss the benefits of taking Prolonged-Rel. venlafaxine CAP and the harmful effects before you start treatment.

■ Prolonged-Rel. venlafaxine CAP are not for use in children and adolescents under 18.

■ Some people who are depressed think of harming or killing themselves. If you start to feel worse, or think of harming or killing yourself, see your doctor or go to a hospital straightaway. See section 2, Thoughts of harming yourself.

■ Prolonged-Rel. venlafaxine CAP will not work straightaway. Some people taking the medicine feel worse before feeling better. Your doctor should see you a few weeks after starting treatment. Tell your doctor if you do not feel better., How to take Prolonged-Rel. venlafaxine CAP.

■ Do not stop taking Prolonged-Rel. venlafaxine CAP without talking to your doctor. If you stop taking Prolonged-Rel. venlafaxine CAP suddenly or miss a dose, you may get withdrawal effects. If you stop taking Prolonged-Rel. venlafaxine CAP.

■ If you are pregnant or planning to get pregnant, talk to your doctor.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

♦ Keep this leaflet. You may need to read it again.

♦ If you have any further questions, ask your doctor or pharmacist.

♦ This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

♦ If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1.What Prolonged-Rel.venlafaxine CAP are and what they are used for.

Prolonged-Rel. venlafaxine CAP belongs to a group of medicines called antidepressants. They are one of a group of medicines called a selective serotonin and noradrenaline reuptake inhibitor (SNRI). It is thought that people who are depressed have lower levels of serotonin and noradrenaline in the brain. It is not fully understood how antidepressants

work, but they may help by increasing the levels of serotonin and noradrenaline in the brain. Prolonged-Rel. venlafaxine CAP are used for the treatment of depression. Your doctor may continue to give you Prolonged-Rel. venlafaxine CAP when you are feeling better to stop your symptoms coming back or stop you becoming depressed in the future. Treating your depression properly is important to help you get better. If not treated your condition may not go away or may be more difficult to treat. You may find it helpful to tell a friend or relative that you are depressed and ask them to read this leaflet as well. You might ask them to tell you if they are worried about any changes in your behaviour.

9.2 What you need to know before you use Prolonged-Rel.venlafaxine CAP

- You have previously had an allergic reaction to venlafaxine or any of the other ingredients listed in section 6 at the end of this leaflet.
- You are also taking or have taken any time within the last 14 days any medicines known as irreversible monoamine oxidase inhibitors (MAOIs), used to treat depression or Parkinson's disease. Taking an irreversible MAOI together with other medicines, including Prolonged-Rel. venlafaxine CAP can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Prolonged-Rel. venlafaxine CAP before you take any MAOI (see also the section "Taking Prolonged-Rel. venlafaxine CAP with other medicines").

If any of these apply to you, tell your doctor or pharmacist immediately, as the capsules may not be suitable for you**.**

Use in children and adolescents under 18 years of age

Prolonged-Rel. venlafaxine CAP should not normally be used in children and adolescents under the age of 18 years.

• Also, you should know that patients under 18 have an increased risk of side effects such as suicidal attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this type of medicine. Despite this, your doctor may occasionally prescribe Prolonged-Rel. venlafaxine CAP for patients under 18 because he/she decides that this is in their best interests.

• If your doctor has prescribed Prolonged-Rel. venlafaxine CAP for someone under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking these capsules.

• The long-term safety effects of Prolonged-Rel. venlafaxine CAP on growth, maturation and cognitive and behavioural development in this age group has not yet been demonstrated.

Take special care and tell your doctor or pharmacist before taking Prolonged-Rel. venlafaxine CAP if:

• You use other medicines that taken concomitantly with Prolonged-Rel. venlafaxine CAP could increase the risk of developing serotonin syndrome (see the section "Taking Prolonged-Rel. venlafaxine CAP with other medicines").

• You have a history of epilepsy, fits or seizures.

• You suffer from, or have a history of, or if someone in your family has had, mania or bipolar disorder (feeling over-excited or euphoric).

• You have eye problems or suffer from, or have a history of, narrow angle glaucoma (increased pressure in the eye).

• You have a tendency to develop bruises or a tendency to bleed easily (history of bleeding disorders), or if you are taking other medicines that may increase the risk of bleeding.

• You have a history of high blood pressure.

• You have a history of aggressive behaviour.

• You have a history of low sodium levels in your blood (hyponatraemia).

• You have a history of heart problems.

• You have been told you have an abnormal heart rhythm

• You have diabetes (your blood glucose levels may be altered due to Prolonged-Rel. venlafaxine CAP, therefore the dosage of your diabetes medicines may need to be adjusted). Prolonged-Rel. venlafaxine CAP may cause a sensation of restlessness or an inability to sit or stand still during the first few weeks of treatment. You should tell your doctor if this happens to you. If you have any of the above, please talk with your doctor before taking Prolonged-Rel. venlafaxine CAP.

Thoughts of harming yourself:

People who are depressed can sometimes have thoughts of harming or killing themselves. These may be increased when you first start taking antidepressants since these medicines take time to work, usually about two weeks but sometimes longer.

- You may be more likely to think like this:

• If you have previously had thoughts about killing or harming yourself.

• If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant. If you get these thoughts at any time, contact your doctor or go to the nearest hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour

• If you have previously had thoughts about killing or harming yourself.

• If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant. If you get these thoughts at any time, contact your doctor or go to the nearest hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour

Dry Mouth

Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries (tooth decay). Therefore, you should take special care in your dental hygiene.

Sexual Problems

Medicines like Prolonged-Rel. venlafaxine CAP (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have continued after stopping treatment.

Taking Prolonged-Rel. venlafaxine CAP with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Your doctor should decide whether you can take Prolonged-Rel. venlafaxine CAP with other medicines.

Do not start or stop taking any medicines, including those bought without a prescription, natural and herbal remedies, before checking with your doctor or pharmacist.

• Monoamine oxidase inhibitors which are used to treat depression or Parkinson's disease must not be taken with Prolonged-Rel. venlafaxine CAP XL. Tell your doctor if you have taken these medicines within the last 14 days. (MAOIs: see the section "Before you take Prolonged-Rel. venlafaxine CAP").

• Serotonin syndrome: Serotonin syndrome, a potentially life-threatening condition may occur with venlafaxine treatment, particularly when taken with other medicines. Examples of these medicines include:

• Triptans (used for migraine)

• Medicines to treat depression, for instance SNRI, SSRIs, tricyclics, or medicines containing lithium

• Medicines containing amphetamines (used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy and obesity)

• Medicines containing linezolid, an antibiotic (used to treat infections)

• Medicines containing moclobemide, a MAOI (used to treat depression)

• Medicines containing sibutramine (used for weight loss)

• Medicines containing tramadol, fentanyl, tapentadol, pethidine, or pentazocine (a painkiller)

• Products containing St. John's Wort (also called Hypericum perforatum, a natural or herbal remedy used to treat mild depression)

• Products containing tryptophan (used for problems such as sleep and depression)

• Medicines containing dextromethorphan (used to treat coughing)

• Medicines containing methadone (used to treat opioid drug addiction or severe pain) • Medicines containing methylene blue (used to treat high levels of met haemoglobin in the blood)

• Antipsychotics (used to treat a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, unclear reasoning and becoming withdrawn) Signs and symptoms of serotonin syndrome may include a combination of the following: restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea, vomiting. In its most severe form, serotonin syndrome can resemble Neuroleptic Malignant Syndrome (NMS). Signs and symptoms of NMS may include a combination of fever, fast heartbeat, sweating, severe muscle stiffness,

confusion, increased muscle enzymes (determined by a blood test). Get medical care right away if you think serotonin syndrome is happening to you. You must tell your doctor if you are taking medicines that can affect your heart rhythm. Examples of these medicines include:

• Antiarrhythmics such as quinidine, amiodarone, sotalol or dofetilide (used to treat abnormal heart rhythm)

• Antipsychotics such as thioridazine (See also Serotonin syndrome above)

• Antibiotics such as erythromycin or moxifloxacin (used to treat bacterial infections)

• Antihistamines (used to treat allergy) the following medicines may also interact with Prolonged-Rel. venlafaxine CAP and should be used with caution. It is especially important to mention to your doctor or pharmacist if you are taking medicines containing:

• Ketoconazole (an antifungal medicine)

• Haloperidol or risperidone (to treat psychiatric conditions)

• Metoprolol (a beta blocker to treat high blood pressure and heart problems)

Taking Prolonged-Rel. venlafaxine CAP with food, drink and alcohol

You should swallow each capsule whole with food and with a drink of water.

You should avoid drinking alcohol while you are taking the capsules. Alcohol may make your symptoms or side effects worse.

Pregnancy, breast-feeding and fertility

You must tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or plan to become pregnant, so that another medicine can be considered. You should use Prolonged-Rel. venlafaxine CAP only after discussing the potential benefits and the potential risks to your unborn child with your doctor. Make sure your midwife and/or doctor know you are on Prolonged-Rel. venlafaxine CAP. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the new born (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby or if your baby is not feeding properly or has trouble breathing, you should contact your midwife and/or doctor immediately. Breast-feeding is not recommended as venlafaxine in Prolonged-Rel. venlafaxine CAP can pass into the breast milk, and there would be risk of an effect on the baby. Therefore, you should discuss this matter with your doctor, and he/she will decide whether you should stop breastfeeding or stop the therapy with Prolonged-Rel. venlafaxine CAP.

Driving and using machines

Possible side effects of Prolonged-Rel. venlafaxine CAP are dizziness, confusion and eye sight changes such as blurred vision. If you get these or feel that your judgement, thinking or co-ordination is affected when you take Prolonged-Rel. venlafaxine CAP do not drive or use machines.

Important information about some of the ingredients of Prolonged-Rel. venlafaxine CAP

This product contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

9.3 How to use take Prolonged-Rel.venlafaxine CAP

Always take Prolonged-Rel. venlafaxine CAP exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual starting dose is one 75 mg capsule a day. However, your doctor may start with a different dose, particularly if you are elderly or have liver or kidney problems. Your doctor may also change your dose during the course of your treatment. Your dose can be raised by your doctor gradually, and if needed, even up to a maximum dose of 375 mg daily for depression. You should swallow each capsule whole at approximately the same time each day, either in the morning or evening. Do not break open, crush or chew the capsules, or put them in water before swallowing. Prolonged-Rel. venlafaxine CAP should be taken with food. Do not stop taking Prolonged-Rel. venlafaxine CAP without talking to your doctor (see the section "If you stop taking Prolonged-Rel. venlafaxine CAP").

If you take more Prolonged-Rel. venlafaxine CAP than you should

Never take more capsules than your doctor tells you. If you accidentally take too many capsules contact your doctor or hospital immediately. Remember to take the packet with you, even if it is empty. The symptoms of a possible overdose may include a rapid heartbeat, changes in level of alertness (ranging from sleepiness to coma), blurred vision, seizures or fits, and vomiting.

If you forget to take Prolonged-Rel. venlafaxine CAP If

You forget to take a capsule, you can take it up to 12 hours after you usually take it, and then take your next capsule at the usual time. If the period after the missed dose is more than 12 hours, you should miss the dose altogether and just take your next capsule at the usual time. Do not take a double dose to make up for a forgotten capsule.

If you stop taking Prolonged-Rel. venlafaxine CAP

Do not stop taking your capsules or reduce the dose without the advice of your doctor, even if you feel better. If your doctor thinks you no longer need Prolonged-Rel. venlafaxine CAP, your dose will be reduced gradually before stopping treatment altogether. Side effects are known to occur when people stop using Prolonged-Rel. venlafaxine CAP, especially when the capsules are stopped suddenly or the dose reduced too quickly. Some patients may experience symptoms such as: tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, feeling or being sick, diarrhoea, nervousness, agitation, confusion, tinnitus (ringing in the ears), tingling, weakness, sweating, fits/ seizures, or flu-like symptoms. These symptoms are generally non-serious and disappear within a few days. Your doctor will advise you on how you should gradually stop Prolonged-Rel. venlafaxine CAP and if you suffer any of these or other symptoms that are troublesome, return to your doctor for further advice.

If you require any further information on Prolonged-Rel. venlafaxine CAP please consult your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, Prolonged-Rel. venlafaxine CAP can cause side effects, although not everybody gets them. Do not be concerned if you see small white granules or balls in your stools after taking Prolonged-Rel. venlafaxine CAP. Inside Prolonged-Rel. venlafaxine CAP capsules are spheroids or small white balls that contain the venlafaxine active ingredient. These spheroids are released from the capsule into your

gastrointestinal tract. As the spheroids travel the length of your gastrointestinal tract, venlafaxine is slowly released. The spheroid "shell" remains undissolved and is eliminated in your stools. Therefore, even though you may see spheroids in your stools, your dose of venlafaxine has been absorbed.
Although the frequency cannot be estimated from the available data cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 2, what you need to know before you take Prolonged-Rel. venlafaxine CAP XL). If any of the following happen, do not take more Prolonged-Rel. venlafaxine CAP XL.
Tell your doctor immediately, or go to the casualty department at your nearest hospital:
Uncommon (may affect up to 1 in 100 people)
• Swelling of the face, mouth, tongue, throat, hands, or feet, and/or a raised itchy rash (hives), trouble swallowing or breathing
Rare (may affect up to 1 in 1,000 people)
• Chest tightness, wheezing, trouble swallowing or breathing
• Severe skin rash, itching or hives (elevated patches of red or pale skin that often itch)
• Signs and symptoms of serotonin syndrome which may include restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea, vomiting.
In its most severe form, serotonin syndrome can resemble Neuroleptic Malignant Syndrome (NMS).
• Signs of infection, such as high temperature, chills, shivering, headaches, and sweating, flu-like symptoms. This may be the result of a blood disorder which leads to an increased risk of infection.
• Severe rash, which may lead to severe blistering and peeling of the skin.
• Unexplained muscle pain, tenderness or weakness. This may be a sign of rhabdomyolysis
Other reported side effects
Very common (affects more than 1 person in 10 users):

- headache; dizziness; drowsiness
- insomnia
- nausea; dry mouth; constipation
- sweating (including night sweats)

Common (affects less than 1 person in 10 users):

- weight loss; weight gain; increased cholesterol
- abnormal dreams; decreased libido; increased muscle tonus; nervousness; pins and needles; tremor; confusion; feeling separated (or detached) from yourself ; agitation; a sensation of restlessness or an inability to sit or stand still; altered taste sensation
- blurred vision; dilated pupils; inability of the eye to automatically change focus from distant to near objects
- increase in blood pressure; flushing; palpitations; fast heartbeat
- yawning; shortness of breath
- appetite decreased; vomiting; diarrhoea
- difficulties passing urine; increased frequency in urination; inability to pass urine

- abnormal ejaculation/orgasm (males); lack of orgasm; erectile dysfunction (impotence); menstrual irregularities such as increased bleeding or increased irregular bleeding
- weakness (asthenia); chills; fatigue
- ringing in the ears (tinnitus)
- mild rash; itching

Uncommon (affects less than 1 person in 100 users):

- bruising; vomiting blood; black tarry stools (faeces) or blood in stools, which can be a sign of internal bleeding
- lack of feeling or emotion; hallucinations; involuntary movement of the muscles; impaired coordination and balance
- feeling dizzy (particularly when standing up too quickly), fainting, decrease in blood pressure
- grinding of the teeth; feeling separated (or detached) from reality; feeling over-excited • abnormal hair loss
- abnormal orgasm (females)
- sensitivity to sunlight
- over activity, racing thoughts and decreased need for sleep (mania)
- inability to control urination
- stiffness, spasms and involuntary movements of the muscles
- slight changes in blood levels of liver enzymes Rare (affects less than 1 person in 1000 users):
- seizures or fits
- coughing, wheezing and shortness of breath which may be accompanied by a high temperature
- disorientation and confusion often accompanied by hallucination (delirium)
- excessive water intake (known as SIADH)
- decrease in blood sodium levels
- severe eye pain and decreased or blurred vision
- abnormal, rapid or irregular heartbeat, which could lead to fainting
- severe abdominal or back pains (which could indicate a serious problem in the gut, liver or pancreas)
- itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis)
- Dystonia - muscle disorder causing twisting movements (dystonia)

Very rare (may affect up to 1 in 10,000 people):

- prolonged bleeding, which may be a sign of reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding
- abnormal breast milk production
- unexpected bleeding, e.g. bleeding gums, blood in the urine or in vomit, or the appearance of unexpected bruises or broken blood vessels (broken veins)
- Tardive dyskinesia - uncontrollable movements of mouth, tongue and limbs(tardive dyskinesia)

Not known (frequency cannot be estimated from the available data):

- Aggression

- Vertigo Prolonged-Rel. venlafaxine CAP sometimes causes unwanted effects which you may not be aware of, such as increases in blood pressure or abnormal heart beat, or slight changes in blood levels of liver enzymes, sodium or rarely cholesterol (fats). More rarely, Prolonged-Rel. venlafaxine CAP may reduce the function of platelets in your blood, leading to increased chance of bruising or bleeding. Therefore, your doctor may wish to do blood tests occasionally, particularly if you have been taking the capsules for a long time

  Reporting of side effects
  If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

  By reporting side effects, you can help provide more information on the safety of this medicine.

9.4 How to store Prolonged-Rel.venlafaxine CAP

Store in dry place at a temperature not exceeding 30 º C.

9.5 Contents of the pack and other information

Each hard gelatin capsule contains:

Venlafaxine Hydrochloride I.P.

Equivalent to venlafaxine 75 mg

(In the form of extended-release pellets)

Approved colours used in hard gelatin capsule shells

Other excipients are Talc, Ethyl cellulose, hydroxy propyl methyl cellulose, methanol, methelyene chloride, ethyl cellulose.

10 Details of manufacturer

Torrent PHARMACEUTICAL LTD.

Vill. Bhud & Makhnu Majra,

The. Baddi-173 205, Dist. Solan (H.P.), India.

11 Details of permission or licence number with date

MNB/05/183 issued on

12 Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/ Prolonged-Rel. venlafaxine CAP mg/NOV-19/01/PI