Public Assessment Report

Decentralised Procedure

Ranfaxiran XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard

Ranfaxine XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard

PL 14894/0519-24

UK/H/1129/01-03/DC

UK/H/1130/01-03/DC

Ranbaxy (UK) Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Ranfaxiran XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard and Ranfaxine XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard (product licence numbers: 14894/0519-24).

These capsules contain the active ingredient venlafaxine hydrochloride. Venlafaxine hydrochloride is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). 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.

The data submitted in support of the applications for Ranfaxiran XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard and Ranfaxine XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about decentralised procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>54</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>67</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>79</td>
</tr>
</tbody>
</table>

- 1 Introduction
- 2 Quality aspects
- 3 Non-clinical aspects
- 4 Clinical aspects
- 5 Overall conclusions
## Module 1

### Information about decentralised procedure

| Name of the product in the Reference Member State | Ranfaxiran XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard Ranfaxine XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard |
| Name of the active substance (INN) | Venlafaxine hydrochloride |
| Pharmacotherapeutic classification (ATC code) | N06 AX16 |
| Pharmaceutical form and strength | Prolonged-Release Capsules, hard; 37.5, 75 and 150mg |
| Reference numbers for the Decentralised Procedure | UK/H/1129/01-03/DC UK/H/1130/01-03/DC |
| Reference Member State | UK |
| Member States concerned | **UK/H/1129/01-03:** BE, BG, CZ, IE, LU, NL, PL, PT, RO, SK **UK/H/1129/02-03 (only):** AT, DE, DK, EE, EL, HU, IS, IT, LT, LV, NO, SE, SI, **UK/H/1130/01-03:** BE, IE, NL, PL |
| Date of start of the procedure | 10 July 2007 |
| End date of decentralised procedure | 19 August 2008 |
| Marketing Authorisation Number | PL 14894/0519-24 |
| Name and address of the authorisation holder | Ranbaxy (UK) Limited 20 Balderton Street, London W1K 6TL United Kingdom |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ranfaxiran XL 37.5 mg prolonged release capsules, hard
Ranfaxine XL 37.5 mg prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Ranfaxiran XL 37.5 mg prolonged release capsule, hard contains 42.43 mg of Venlafaxine Hydrochloride equivalent to 37.5 mg of Venlafaxine

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged-Release Capsule, hard

Ranfaxiran XL 37.5 mg prolonged release capsules, hard are Size “2” capsule with grey opaque cap and pink opaque body imprinted with RVn on the cap and 37.5 on the body in black ink

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

4.2 Posology and method of administration
Major depressive episodes

The recommended starting dose for Ranfaxiran XL 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. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

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

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

**Use in elderly patients**

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

**Use in children and adolescents under the age of 18 years**

Venlafaxine is not recommended for use in children and adolescents.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

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

**Use in patients with hepatic impairment**

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

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

**Use in patients with renal impairment**

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

**Withdrawal symptoms seen on discontinuation of venlafaxine**

Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

For oral use.
It is recommended that Ranfaxiran XL 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 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Ranfaxiran XL 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.

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

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

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which venlafaxine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients, and in particular those at high risk, should accompany drug therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be
alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age

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

Serotonin syndrome

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

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

Narrow-angle glaucoma

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

Blood pressure

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

Heart rate

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

Cardiac disease and risk of arrhythmia
Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

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

**Convulsions**

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

**Hyponatraemia**

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

**Abnormal bleeding**

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

**Serum cholesterol**

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

**Co-administration with weight loss agents**

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

**Mania/hypomania**

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

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

Discontinuation of treatment

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 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).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)

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

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

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

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

Serotonin syndrome

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

If concomitant treatment of venlafaxine with an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS-active substances

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

Ethanol

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

Effect of other medicinal products on venlafaxine

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

Effect of venlafaxine on other medicinal products

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

Diazepam
Venlafaxine has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyl-diazepam. 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 $C_{\text{max}}$ for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

4.6 Pregnancy and lactation

Pregnancy

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

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

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

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

Lactation

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

4.7 Effects on ability to drive and use machines

Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

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

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

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), not known (cannot be estimated from the available data).
<table>
<thead>
<tr>
<th>Body System</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological/Lymphatic</td>
<td></td>
<td>Ecchymosis, Gastrointestinal haemorrhage</td>
<td></td>
<td>Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopenia, Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopenia)</td>
<td></td>
</tr>
<tr>
<td>Metabolic/Nutritional</td>
<td>Serum cholesterol increased, Weight loss</td>
<td>Weight gain</td>
<td></td>
<td>Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased</td>
<td></td>
</tr>
<tr>
<td>Nervous</td>
<td>Dry mouth (10.0%), Headache (30.3%)*</td>
<td>Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Confusion, Depersonalisation</td>
<td>Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance</td>
<td>Akathisia/ Psychomotor restlessness, Convulsion, Manic reaction</td>
<td>Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinesia), Tardive dyskinesia, Suicidal ideation and behaviours**</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Abnormality of accommodation, Mydriasis, Visual disturbance,</td>
<td>Altered taste sensation, Tinnitus</td>
<td></td>
<td>Angle-closure glaucoma</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations</td>
<td>Postural hypotension, Syncope, Tachycardia</td>
<td></td>
<td>Hypotension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)</td>
<td></td>
</tr>
<tr>
<td>Body System</td>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not Known</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>-------------------------</td>
<td>---------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>Yawning</td>
<td></td>
<td></td>
<td>Pulmonary eosinophilia</td>
</tr>
<tr>
<td>Digestive</td>
<td>Nausea (20.0%)</td>
<td>Appetite decreased (anorexia), Constipation, Vomiting</td>
<td>Bruxism, Diarrhoea</td>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Skin</td>
<td>Sweating (including night sweats) [12.2%]</td>
<td>RASH, Alopecia</td>
<td></td>
<td></td>
<td>Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstral disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria</td>
<td>Abnormal orgasm (females), Urinary retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Asthenia (fatigue), Chills</td>
<td>Photosensitivity reaction</td>
<td></td>
<td></td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

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

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

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients, they may be severe and/or prolonged. It is therefore advised...
that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

**Paediatric patients**

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).

In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

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

### 4.9 Overdose

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

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

**Recommended treatment**

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants - ATC code: NO6A X16.
The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, 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.

**5.2 Pharmacokinetic properties**

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

**Absorption**

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

**Distribution**

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

**Metabolism**

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

**Elimination**

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1.3±0.6 L/h/kg and 0.4±0.2 L/h/kg, respectively.

**Special populations**

**Age and gender**

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

**CYP2D6 extensive/poor metabolisers**

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

**Patients with hepatic impairment**

In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were prolonged compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).
Patients with renal impairment
In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance reduced by about 57% compared to normal subjects, while ODV elimination half-life was prolonged by about 142% and clearance reduced by about 56%. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

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

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown. These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core Spheroid Composition
Cellulose, microcrystalline
Hypromellose

Modified Release coating
Ethyl cellulose
Povidone (K 30)
Triacetin
Talc

Capsule Shell: Grey opaque cap and pink opaque body

Body
Iron Oxide Red (E 172)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate

Cap
FD & C Blue 1 (E 133)
D & C Yellow 10 (E 104)
FD & C Red 40 (E 129)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate
Black Printing Ink:
Shellac
Propylene glycol
Strong ammonia solution
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 Years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
PVC Blister pack
White opaque PVC film with the backing of hard tempered, heat sealable aluminum foil of printable quality coated with heat sealed lacquer on inner side.

7, 10, 14 20, 28, 30, 50, 56, 60, 100

For healthcare professions only
HDPE bottle pack: 100
White opaque high-density polyethylene bottle (HDPE) with fine ribbed screw cap with induction seal liner

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
UK

8 MARKETING AUTHORITY NUMBER
PL 14894/0519
PL 14894/0522
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2008

10 DATE OF REVISION OF THE TEXT
03/11/2008

1 NAME OF THE MEDICINAL PRODUCT
Ranfaxiran XL 75 mg prolonged release capsules, hard
Ranfaxine XL 75 mg prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Ranfaxiran XL 75 mg prolonged release capsule, hard contains 84.85 mg venlafaxine hydrochloride, equivalent to 75mg Venlafaxine

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged-Release Capsule, hard

Ranfaxiran XL 75 mg prolonged release capsules, hard are Size “1” capsule with pink opaque cap and body imprinted with RVn on the cap and 75 on the body in black ink

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

4.2 Posology and method of administration

Major depressive episodes

The recommended starting dose for Ranfaxiran XL 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. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.
Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation (see section 4.4). The lowest effective dose should be maintained.

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

Antidepressive medicinal products should continue for at least six months following remission.  
*Use in elderly patients*

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

*Use in children and adolescents under the age of 18 years*

Venlafaxine is not recommended for use in children and adolescents.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

The efficacy and safety of venlafaxine for other indications in children and adolescents under the age of 18 have not been established.  
*Use in patients with hepatic impairment*

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

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

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

Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

For oral use.

It is recommended that Ranfaxiran XL 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 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Ranfaxiran XL 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.

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

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

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which venlafaxine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients, and in particular those at high risk, should accompany drug therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

*Use in children and adolescents under 18 years of age*

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

*Serotonin syndrome*

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

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

*Narrow-angle glaucoma*

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

*Blood pressure*

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

*Heart rate*

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

*Cardiac disease and risk of arrhythmia*

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

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

*Convulsions*

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

*Hyponatraemia*

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

*Abnormal bleeding*

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

*Serum cholesterol*

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

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

**Mania/hypomania**

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

**Aggression**

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

**Discontinuation of treatment**

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 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).

**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.
4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)

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

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

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

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

Serotonin syndrome

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

If concomitant treatment of venlafaxine with an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS-active substances

The risk of using venlafaxine in combination with other CNS-active substances has not been systematically evaluated. Consequently, caution is advised when venlafaxine is taken in combination with other CNS-active substances.
Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

**Effect of other medicinal products on venlafaxine**

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

**Effect of venlafaxine on other medicinal products**

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

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

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

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

**Risperidone**  
Venlafaxine increased the risperidone AUC by 50%, but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.
Metoprolol
Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicinal products resulted in an increase of plasma concentrations of metoprolol by approximately 30-40% without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of venlafaxine and metoprolol.

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

4.6 Pregnancy and lactation

Pregnancy

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

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

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

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

Lactation

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

4.7 Effects on ability to drive and use machines

Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine should be cautioned about their ability to drive or operate hazardous machinery.
4.8 Undesirable effects

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

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

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological/Lymphatic</td>
<td></td>
<td></td>
<td>Ecchymosis, Gastrointestinal haemorrhage</td>
<td></td>
<td>Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopenia, Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia)</td>
</tr>
<tr>
<td>Metabolic/Nutritional</td>
<td>Serum cholesterol increased, Weight loss</td>
<td>Weight gain</td>
<td>Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous</td>
<td>Dry mouth (10.0%), Headache (30.3%)*</td>
<td>Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation</td>
<td>Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance</td>
<td>Akathisia/ Psychomotor restlessness, Convulsion, Manic reaction</td>
<td>Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinaesia), Tardive dyskinaesia, Suicidal ideation and behaviours**</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Abnormality of accommodation, Mydriasis, Visual disturbance,</td>
<td>Altered taste sensation, Tinnitus</td>
<td></td>
<td></td>
<td>Angle-closure glaucoma</td>
</tr>
<tr>
<td>Body System</td>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not Known</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>Hypertension, Vasodilatation</td>
<td>Postural hypotension, Syncope, Tachycardia</td>
<td>Hyptension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mostly hot flashes/flushes), Palpitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulmonary eosinophilia</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>Nausea (20.0%)</td>
<td>Apetite decreased (anorexia), Constipation, Vomiting</td>
<td>Bruxism, Diarrhoea</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Sweating (including night sweats) [12.2%]</td>
<td>Rash, Alopecia</td>
<td></td>
<td>Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td>Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria</td>
<td>Abnormal orgasm (females), Urinary retention</td>
<td>Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td>Asthenia (fatigue), Chills</td>
<td>Photosensitivity reaction</td>
<td></td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

*In pooled clinical trials, the incidence of headache was 30.3% with venlafaxine versus 31.3% with placebo.
Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients, they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Paediatric patients

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).

In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

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

4.9 Overdose

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

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

Recommended treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antidepressants - ATC code: NO6A X16.

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, 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.
5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1.3±0.6 L/h/kg and 0.4±0.2 L/h/kg, respectively.

Special populations

Age and gender

Subject age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.
CYP2D6 extensive/poor metabolisers
Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

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

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

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

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown. These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core Spheroid Composition
Cellulose, microcrystalline
Hypermellose
Modified Release coating
Ethyl cellulose
Povidone (K 30)
Triacetin
Talc

Capsule Shell: Pink Opaque
Body
Iron Oxide Red (E 172)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate

Cap
Iron Oxide Red (E 172)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate

Black Printing Ink:
Shellac
Propylene glycol
Strong ammonia solution
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 Years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
PVC Blister pack
White opaque PVC film with the backing of hard tempered, heat sealable aluminum foil of printable quality coated with heat sealed lacquer on inner side.

7, 10, 14 20, 28, 30, 50, 56, 60, 100

For healthcare professions only
HDPE bottle pack: 100
White opaque high-density polyethylene bottle (HDPE) with fine ribbed screw cap with induction seal liner

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0520
PL 14894/0523

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2008

10 DATE OF REVISION OF THE TEXT
03/11/2008

1 NAME OF THE MEDICINAL PRODUCT
Ranfaxiran XL 150 mg prolonged release capsules, hard
Ranfaxine XL 150 mg prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Ranfaxiran XL 150 mg prolonged release capsule, hard contains 169.71 mg venlafaxine hydrochloride, equivalent to 150mg Venlafaxine

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged- Release Capsule, hard

Ranfaxiran XL 150 mg prolonged release capsules, hard are Size “0” capsules with caramel opaque cap and body imprinted with RVn on the cap and 150 on the body in black ink

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.
4.2 Posology and method of administration

Major depressive episodes

The recommended starting dose for Ranfaxiran XL 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. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

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

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

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

Use in elderly patients

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

Use in children and adolescents under the age of 18 years

Venlafaxine is not recommended for use in children and adolescents.

Controlled clinical studies in children and adolescents with major depressive disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.4 and 4.8).

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

Use in patients with hepatic impairment

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

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

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

Withdrawal symptoms seen on discontinuation of venlafaxine

Abrupt discontinuation should be avoided. When stopping treatment with venlafaxine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

For oral use.

It is recommended that Ranfaxiran XL 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 37.5 mg twice daily may be switched to venlafaxine prolonged-release capsules 75 mg once daily. Individual dosage adjustments may be necessary.

Ranfaxiran XL 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.

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

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

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such
improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which venlafaxine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients, and in particular those at high risk, should accompany drug therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age

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

Serotonin syndrome

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

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

Narrow-angle glaucoma

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

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

**Heart rate**

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

**Cardiac disease and risk of arrhythmia**

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

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

**Convulsions**

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

**Hyponatraemia**

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

**Abnormal bleeding**

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

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

**Co-administration with weight loss agents**

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

**Mania/hypomania**

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

**Aggression**

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

**Discontinuation of treatment**

Withdrawal symptoms, when treatment is discontinued, are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 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).

**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.

4.5 Interaction with other medicinal products and other forms of interaction

*Monoamine Oxidase Inhibitors (MAOI)*

Irreversible non-selective MAOIs

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

Reversible, selective MAO-A inhibitor (moclobemide)

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

Reversible, non-selective MAOI (linezolid)

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

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

**Serotonin syndrome**

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

If concomitant treatment of venlafaxine with an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of venlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).
CNS-active substances

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

Ethanol

Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active substances, patients should be advised to avoid alcohol consumption.

Effect of other medicinal products on venlafaxine

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

Effect of venlafaxine on other medicinal products

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

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

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

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

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

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

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

### 4.6 Pregnancy and lactation

**Pregnancy**

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

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

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

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

**Lactation**

Venlafaxine and its active metabolite, O-desmethylvenlafaxine, are excreted in breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision to continue/discontinue breast-feeding or to continue/discontinue therapy with Ranfaxiran XL should be made, taking into account the benefit of breast-feeding to the child and the benefit of Ranfaxiran XL therapy to the woman.
4.7 Effects on ability to drive and use machines
Any psychoactive medicinal product may impair judgment, thinking, and motor skills. Therefore, any patient receiving venlafaxine should be cautioned about their ability to drive or operate hazardous machinery.

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

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

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological/Lymphatic</td>
<td></td>
<td></td>
<td>Ecchymosis, Gastrointestinal haemorrhage</td>
<td></td>
<td>Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopenia, Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopenia)</td>
</tr>
<tr>
<td>Metabolic/Nutritional</td>
<td>Serum cholesterol increased, Weight loss</td>
<td>Weight gain</td>
<td></td>
<td>Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased</td>
<td></td>
</tr>
<tr>
<td>Body System</td>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not Known</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nervous</td>
<td>Dry mouth (10.0%), Headache (30.3%)*</td>
<td>Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation</td>
<td>Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance</td>
<td>Akathisia/ Psychomotor restlessness, Convulsion, Manic reaction</td>
<td>Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinesia), Tardive dyskinesia, Suicidal ideation and behaviours**</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Abnormality of accommodation, Mydriasis, Visual disturbance,</td>
<td></td>
<td>Altered taste sensation, Tinnitus</td>
<td></td>
<td>Angle-closure glaucoma</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations</td>
<td>Postural hypotension, Syncope, Tachycardia</td>
<td></td>
<td>Hypotension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Yawning</td>
<td></td>
<td></td>
<td>Pulmonary eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Digestive</td>
<td>Nausea (20.0%)</td>
<td>Appetite decreased (anorexia), Constipation, Vomiting</td>
<td>Bruxism, Diarrhoea</td>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Skin</td>
<td>Sweating (including night sweats) [12.2%]</td>
<td>Rash, Alopecia</td>
<td></td>
<td>Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td>Body System</td>
<td>Very Common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not Known</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td>Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria</td>
<td>Abnormal orgasm (females), Urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td>Abnormal orgasm (females), Urinary retention</td>
<td>Photosensitivity reaction</td>
<td>Anaphylaxis</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients, they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

**Paediatric patients**

In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (ages 6 to 17) was similar to that seen for adults. As with adults, decreased appetite, weight loss, increased blood pressure, and increased serum cholesterol were observed (see section 4.4).

In paediatric clinical trials the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

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

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

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

Recommended treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, 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.

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

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

**Elimination**

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1.3±0.6 L/h/kg and 0.4±0.2 L/h/kg, respectively.

**Special populations**

**Age and gender**

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

**CYP2D6 extensive/poor metabolisers**

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

**Patients with hepatic impairment**

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

**Patients with renal impairment**

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

5.3 Preclinical safety data

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

Animal studies regarding reproductive toxicity have found in rats a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation. The cause of these deaths is unknown. These effects occurred at 30 mg/kg/day, 4 times the human daily dose of 375 mg of venlafaxine (on an mg/kg basis). The no-effect dose for these findings was 1.3 times the human dose. The potential risk for humans is unknown.
Reduced fertility was observed in a study in which both male and female rats were exposed to ODV. This exposure was approximately 1 to 2 times that of a human venlafaxine dose of 375 mg/day. The human relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Spheroid Composition
Cellulose, microcrystalline
Hypermellose

Modified Release coating
Ethyl cellulose
Povidone (K 30)
Triacetin
Talc

Capsule Shell: Caramel Opaque,
Body
Iron Oxide Red (E172)
Iron Oxide Yellow (E 172)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate

Cap
Iron Oxide Red (E172)
Iron Oxide Yellow (E 172)
Titanium Dioxide (E171)
Gelatin
Sodium Lauryl Sulfate

Black Printing Ink:
Shellac
Propylene glycol
Strong ammonia solution
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 Years
6.4  **Special precautions for storage**
This medicinal product does not require any special storage conditions.

6.5  **Nature and contents of container**
**PVC Blister pack**
White opaque PVC film with the backing of hard tempered, heat sealable aluminum foil of printable quality coated with heat sealed lacquer on inner side.

7, 10, 14 20, 28, 30, 50, 56, 60, 100

For healthcare professions only
**HDPE bottle pack: 100**
White opaque high-density polyethylene bottle (HDPE) with fine ribbed screw cap with induction seal liner.

Not all pack sizes may be marketed.

6.6  **Special precautions for disposal**
No special requirements.

7  **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
UK

8  **MARKETING AUTHORISATION NUMBER(S)**
PL 14894/0521
PL 14894/0524

9  **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
03/11/2008

10 **DATE OF REVISION OF THE TEXT**
03/11/2008
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

RANFAXIRAN XL 37.5 MG
PROLONGED RELEASE CAPSULES, HARD
RANFAXIRAN XL 75 MG
PROLONGED RELEASE CAPSULES, HARD
RANFAXIRAN XL 150 MG
PROLONGED RELEASE CAPSULES, HARD

Venlafaxine

Read all this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or your pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ranfaxiran XL is and what it is used for
2. Before you take Ranfaxiran XL
3. How to take Ranfaxiran XL
4. Possible side effects
5. How to store Ranfaxiran XL
6. Further information

1. WHAT RANFAXIRAN XL IS AND WHAT IT IS USED FOR

Ranfaxiran XL is an antidepressant that belongs to a group of medicines known as serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression. 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. Ranfaxiran XL is a treatment for adults with depression. Treating depression properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and more difficult to treat. Ranfaxiran XL may be prescribed for conditions not listed here. Ask your doctor or pharmacist if you have further questions.

2. BEFORE YOU TAKE RANFAXIRAN XL

Do not take Ranfaxiran XL
• If you are allergic to venlafaxine or any of the other ingredients of Ranfaxiran XL.
• If 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 Ranfaxiran XL, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Ranfaxiran XL before you take any MAOI (see also the sections "Serotonin syndrome" and "Taking other medicines").

Take special care with Ranfaxiran XL
• If you use other medicines that can concomitantly with Ranfaxiran XL could increase the risk of developing serotonin syndrome (see the section "Taking other medicines").
• If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
• If you have a history of high blood pressure.
• If you have a history of heart problems.
• If you have a history of fits (seizures).
• If you have a history of low sodium levels in your blood (hyponatraemia).
• If 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.
• If your cholesterol levels get higher.
• If you have a history of, or if someone in your family has had, manic or bipolar disorder (feeling overexcited or euphoric).
• If you have a history of aggressive behaviour.

Ranfaxiran XL may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

If any of these conditions apply to you, please talk with your doctor before taking Ranfaxiran XL.

Thoughts of suicide and worsening of your depression

If you are depressed, you can sometimes have thoughts of harming or killing yourself. These may be increased when you first start taking antidepressants, since these medicines all 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 yourself or harming yourself.**
- **If you are a young adult.** Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a 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. Therefore, you should take special care in your dental hygiene.

**Use in children and adolescents under 18 years of age**

Ranfaxirax XL should not normally be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side effects, such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Your doctor may prescribe Ranfaxirax XL for patients under 16 because he/she decides that this is in their best interests. If your doctor has prescribed Ranfaxirax XL for a patient 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 Ranfaxirax XL. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Ranfaxirax XL in this age group has not yet been demonstrated.

**Taking 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 Ranfaxirax XL 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 (MAOIs):** see the section “Before you take Ranfaxirax XL”.
- **Serotonin syndrome:** Serotonin syndrome, a potentially life-threatening condition (see the section “Possible Side Effects”), 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 SNRIs, SSRIs, triyclics, or medicines containing lithium
  - Medicines containing linezolid, an antibiotic (used to treat infections)
  - Medicines containing moclobemide, a reversible MAOI (used to treat depression)
  - Medicines containing sibutramine (used for weight loss)
  - Medicines containing tramadol (a pain-killer)
  - 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)

Signs and symptoms of serotonin syndrome may include a combination of the following: restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhcea, coma, nausea, vomiting. Get medical care right away if you think serotonin syndrome is happening to you.

The following medicines may also interact with Ranfaxirax XL 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 Ranfaxirax XL with food and drink**

Ranfaxirax XL should be taken with food.

You should avoid alcohol while you are taking Ranfaxirax XL.

**Pregnancy and breast-feeding**

Tell your doctor if you become pregnant, or you are trying to become pregnant. You should use Ranfaxirax XL only after discussing the potential benefits and the potential risks to your unborn child with your doctor.

If you are taking Ranfaxirax XL during pregnancy, let your doctor know, as your baby might have some symptoms when it is born. These symptoms usually begin during the first 24 hours after the baby is born. They include not feeding properly and trouble with breathing. If your baby has these symptoms when it is born and you are concerned, contact your doctor and/or midwife who will be able to advise you.

Venlafaxine passes into breast milk. There is a risk of an effect on the baby. Therefore, you should discuss the matter with your doctor, and he/she will decide whether you should stop breast-feeding or stop the therapy with Ranfaxirax XL.

**Driving and using machines**

Do not drive or use any tools or machines until you know how Ranfaxirax XL affects you.

3. **HOW TO TAKE RANFAXIRAX XL**

Always take Ranfaxirax XL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual recommended starting dose for treatment of depression is 75 mg per day. The dose can be raised by your doctor gradually, and if needed, even up to a maximum dose of 375 mg daily.

Take Ranfaxirax XL approximately the same time each day, either in the morning or in the evening. Capsules must be swallowed whole with fluid and not opened, crushed, chewed or dissolved.

Ranfaxirax XL should be taken with food.

If you have liver or kidney problems, talk to your doctor, since your dose may need to be different.

Do not stop taking without talking to your doctor (see the section “If you stop taking Ranfaxirax XL”).
If you take more Ranfaxiran XL than you should
Call your doctor or pharmacist immediately if you take more than the amount of Ranfaxiran XL prescribed by your doctor.
The symptoms of a possible overdose may include a rapid heart beat, changes in level of alertness (ranging from sleepiness to coma), blurred vision, seizures or fits, and vomiting.

If you forget to take Ranfaxiran XL
If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take more than the daily amount of Ranfaxiran XL that has been prescribed for you in one day.

If you stop taking Ranfaxiran XL
Do not stop taking your treatment or reduce the dose without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Ranfaxiran XL, he/she may ask you to reduce your dose slowly before stopping treatment altogether. Side effects are known to occur when people stop using Ranfaxiran XL, especially when Ranfaxiran XL is stopped suddenly or the dose is reduced too quickly. Some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, nausea, diarrhoea, nervousness, agitation, confusion, ringing in the ears, tingling or rarely electric shock sensations, weakness, sweating, seizures, or flu-like symptoms.

Your doctor will advise you on how you should gradually discontinue Ranfaxiran XL treatment. If you experience any of these or other symptoms that are troublesome, ask your doctor for further advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ranfaxiran XL 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 Ranfaxiran XL. Inside Ranfaxiran XL 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.

Allergic reactions
If any of the following happen, do not take more Ranfaxiran XL. Tell your doctor immediately, or go to the casualty department at your nearest hospital:
• Chest tightness, wheezing, trouble swallowing or breathing
• Swelling of the face, throat, hands, or feet
• Feeling nervous or anxious, dizziness, throbbing sensations, sudden reddening of the skin and/or a warm feeling
• Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious side effects
If you notice any signs of the following, you may need urgent medical attention:
• Heart problems, such as fast or irregular heart rate, increased blood pressure
• Eye problems, such as blurred vision, dilated pupils
• Nerve problems, such as dizziness, pins and needles, movement disorder, seizures or fits
• Psychiatric problems, such as hyperactivity and euphoria
• Treatment withdrawal (see the section “HOW TO TAKE RANFAXIRAN XL, if you stop taking Ranfaxiran XL”).

Complete side effect listing
The frequency (likelihood of occurring) of side effects is classified as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Affects more than 1 user in 10</td>
</tr>
<tr>
<td>Common</td>
<td>Affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare</td>
<td>Affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>Frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

• Blood disorders
  **Uncommon:** bruising; black tarry stools (faeces) or blood in stools, which can be a sign of internal bleeding
  **Not known:** reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding; blood
disorders which may lead to an increased risk of infection

- **Metabolism/nutritional disorders**
  - Common: weight loss; increased cholesterol
  - Uncommon: weight gain
  - Not known: slight changes in blood levels of liver enzymes; decrease in blood sodium levels; itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis); confusion, excessive water intake (known as SIADH); abnormal breast milk production

- **Nervous system disorders**
  - Very common: dry mouth; headache
  - Common: abnormal dreams; decreased libido; dizziness; increased muscle tone; insomnia; nervousness; pins and needles; sedation; tremor; confusion; feeling separated (or detached) from yourself and reality
  - Uncommon: lack of feeling or emotion; hallucinations; involuntary movement of the muscles; agitation; impaired coordination and balance
  - Rare: a sensation of restlessness or an inability to sit or stand still; seizures or fits; feeling over-excited or euphoric
  - Not known: a high temperature with rigid muscles, confusion or agitation, and sweating, or if you experience jerky muscle movements which you can't control, these may be symptoms of serious conditions known as neuroleptic malignant syndrome; euphoric feelings, drowsiness, sustained rapid eye movement, clumsiness, restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotoninergic syndrome; disorientation and confusion often accompanied by hallucination (delirium); stiffness, spasms and involuntary movements of the muscles; thoughts of harming or killing yourself

- **Sight and hearing disorders**
  - Common: blurred vision
  - Uncommon: altered taste sensation; ringing in the ears (tinnitus)
  - Not known: severe eye pain and decreased or blurred vision

- **Heart or circulation disorders**
  - Common: increase in blood pressure; flushing; palpitations
  - Uncommon: feeling dizzy (particularly when standing up too quickly), fainting, fast heartbeat
  - Not known: decrease in blood pressure; abnormal, rapid or irregular heartbeat, which could lead to fainting

- **Breathing disorders**
  - Common: yawning
  - Not known: coughing, wheezing, shortness of breath and a high temperature, which are symptoms of inflammation of the lungs associated with an increase in white blood cells (pulmonary eosinophilia)

- **Digestive disorders**
  - Very common: nausea
  - Common: appetite decreased; constipation; vomiting
  - Uncommon: grinding of the teeth; diarrhoea
  - Not known: severe abdominal or back pains (which could indicate a serious problem in the gut, liver or pancreas)

- **Skin disorders**
  - Very common: sweating (including night sweats)
  - Uncommon: rash; abnormal hair loss
  - Not known: skin rash, which may lead to severe blistering and peeling of the skin; itching; mild rash

- **Muscle disorders**
  - Not known: unexplained muscle pain, tenderness or weakness (rhabdomyolysis)

- **Urinary system disorders**
  - Common: difficulties passing urine; increased frequency in urination
  - Uncommon: inability to pass urine

- **Reproductive and sexual disorders**
  - Common: abnormal ejaculation/orgasm (males); lack of orgasm; erectile dysfunction (impotence); menstrual irregularities such as increased bleeding or increased irregular bleeding
  - Uncommon: abnormal orgasm (females)
MHRA PAR; RANFAXIRAN XL 37.5 MG, 75 MG AND 150 MG PROLONGED RELEASE CAPSULES, HARD, PL 14894/0519-24

• General
  Common: weakness (asthenia); chills
  Uncommon: sensitivity to sunlight
  Not known: swollen face or tongue, shortness of breath or difficulty breathing, often with skin rashes (this may be a serious allergic reaction)

Ranfaxiran XL sometimes causes unwanted effects that you may not be aware of, such as increases in blood pressure or abnormal heart beat, slight changes in blood levels or liver enzymes, sodium or cholesterol. More rarely, Ranfaxiran XL may reduce the function of platelets in your blood, leading to an increased risk of bruising or bleeding. Therefore, your doctor may wish to do blood tests occasionally, particularly if you have been taking Ranfaxiran XL for a long time.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RANFAXIRAN XL

Keep out of the reach and sight of children.
Do not use Ranfaxiran XL after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ranfaxiran XL contains
Ranfaxiran XL 37.5 mg prolonged release capsule, hard
The active substance is venlafaxine.
Each prolonged release capsule, hard contains 42.43 mg of Venlafaxine Hydrochloride equivalent to 37.5 mg of Venlafaxine.
Other ingredients in these capsules are:
Core Spheroid Composition: Cellulose, microcrystalline, Hypromellose,
Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

Capsule Shell:
Body
Iron Oxide Red (E 172)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Cap
FD & C Blue 1 (E 133)
D & C Yellow 10 (E 104)
FD & C Red 40 (E 129)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Ranfaxiran XL 75 mg prolonged release capsule, hard
The active substance is venlafaxine.
Each prolonged release capsule, hard contains 84.65 mg of Venlafaxine Hydrochloride equivalent to 75 mg of Venlafaxine respectively.
Other ingredients in these capsules are:
Core Spheroid Composition: Cellulose, microcrystalline, Hypromellose,
Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

Capsule Shell:
Body
Iron Oxide Red (E 172)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Cap
Iron Oxide Red (E 172)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Ranfaxiran XL 150 mg prolonged release capsules, hard
The active substance is venlafaxine.
Each prolonged release capsule, hard contains 169.71 mg of Venlafaxine Hydrochloride equivalent to 150 mg of Venlafaxine respectively.
Core Spheroid Composition: Cellulose, microcrystalline, Hypromellose,
Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

Capsule Shell:
Body
Iron Oxide Red (E 172)
Iron Oxide Yellow (E 172)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Cap
Iron Oxide Red (E 172)
Iron Oxide Yellow (E 172)
Titanium Dioxide (E 171)
Gelatin
Sodium Lauryl Sulfate
Black Printing Ink:
Shellac
Propylene glycol
Strong ammonia solution
Black iron oxide (E 172)
Potassium hydroxide

MHRA PAR  ARD  59
What Ranfaxiran XL looks like and contents of the pack

Ranfaxiran XL is available in three strengths 37.5mg, 75mg and 150mg. Each strength of Ranfaxiran XL has a different marking/debossing on one side and is plain on the other side.

Ranfaxiran XL 37.5 mg prolonged release capsule, hard
The 37.5 mg capsules are Size "2" capsule with grey opaque cap and pink opaque body imprinted with RVn on the cap and 37.5 on the body in black ink.
The 37.5 mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 capsules are also available.
Not all pack sizes may be marketed.

Ranfaxiran XL 75 mg prolonged release capsule, hard
The 75 mg capsules are Size "1" capsule with pink opaque cap and body imprinted with RVn on the cap and 75 on the body in black ink.
The 75mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 of capsules are also available.

Ranfaxiran XL 150 mg prolonged release capsule, hard
The 150 mg capsules "Size 0" capsules with caramel opaque cap and body imprinted with RVn on the cap and 150 on the body in black ink.
The 150mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 of capsules are also available.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom

Manufacturer:
Ranbaxy Ireland Limited
Spafield, Cork Road,
Cashel, Co-Tipperary
Ireland

Cemelog - BRF Kft
2040 Budaors VasU 2 u. 2
Hungary

Terapia S.A.,
124 Fabricii Street,
Cluj-Napoca 400 632,
Romania

This medicinal product is authorized in the Member States of the EEA under the following names:
Austria, Belgium, Denmark, Luxembourg Netherlands, Norway, Sweden Venlafaxin Ranbaxy
Bulgaria- Venlift XL
Czech Republic, Slovakia - Ranfaxiran prolong
DE- Venlafaxin BASICS
Estonia Lithuania, Latvia - Venlobax
Greece- Venlafaxine
Hungary, Ireland- Venlift XL
Italy- Venlafaxina Ranbaxy Italia
Iceland Venlafaxin Ranbaxy
Poland- Venlabax Ranbaxy
Portugal- Venlafaxina Ranbaxy
Romania- Adoxa EP
Slovenia- Venlafaksin
United Kingdom- Ranfaxiran XL

This leaflet was last approved in October 2008
Read all this leaflet carefully before you start taking this medicine.
* Keep this leaflet. You may need to read it again.
* If you have any further questions, ask your doctor or your pharmacist.
* This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
* If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ranfaxine XL is and what it is used for
2. Before you take Ranfaxine XL
3. How to take Ranfaxine XL
4. Possible side effects
5. How to store Ranfaxine XL
6. Further information

1. WHAT RANFAXINE XL IS AND WHAT IT IS USED FOR

Ranfaxine XL is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression. 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. Ranfaxine XL is a treatment for adults with depression. Treating depression properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and more difficult to treat. Ranfaxine XL may be prescribed for conditions not listed here. Ask your doctor or pharmacist if you have further questions.

2. BEFORE YOU TAKE RANFAXINE XL

Do not take Ranfaxine XL
* If you are allergic to venlafaxine or any of the other ingredients of Ranfaxine XL.
* If 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 Ranfaxine XL, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Ranfaxine XL before you take any MAOI (see also the sections “Serotonin syndrome” and “Taking other medicines”).

Take special care with Ranfaxine XL
* If you use other medicines that taken concomitantly with Ranfaxine XL could increase the risk of developing serotonin syndrome (see the section “Taking other medicines”).
* If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
* If you have a history of high blood pressure.
* If you have a history of heart problems.
* If you have a history of fits (seizures).
* If you have a history of low sodium levels in your blood (hyponatraemia).
* If 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.
* If your cholesterol levels get higher.
* If you have a history of, or if someone in your family has had, mania or bipolar disorder (feeling over-excited or euphoric).
* If you have a history of aggressive behaviour.

Ranfaxine XL may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

If any of these conditions apply to you, please talk with your doctor before taking Ranfaxine XL.

Thoughts of suicide and worsening of your depression
If you are depressed, you can sometimes have thoughts of harming or killing yourself. These may be increased when you first start taking antidepressants, since these medicines all 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 yourself or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.
- If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a 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. Therefore, you should take special care in your dental hygiene.

Use in children and adolescents under 18 years of age

Ranfaxine XL should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side effects, such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Ranfaxine XL for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Ranfaxine XL for a patient 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 Ranfaxine XL. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Ranfaxine XL in this age group has not yet been demonstrated.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription.

Your doctor should decide whether you can take Ranfaxine XL with other medicines.

- Do not start or stop taking any medicines, including those bought without a prescription, natural and herbal remedies, or prescription-only medicines, without first checking with your doctor or pharmacist.
-Monoamine oxidase inhibitors (MAOIs: see the section "Before you take Ranfaxine XL").
- Serotonin syndrome: Serotonin syndrome, a potentially life-threatening condition (see the section "Possible Side Effects").
- Triptans (used for migraine).
- Medicines to treat depression, for instance SNRIs, SSRIs, tricyclics, or medicines containing lithium.
- Medicines containing linezolid, an antibiotic used to treat infections.
- Medicines containing moclobemide, a reversible MAO I (used to treat depression).
- Medicines containing sibutramine (used for weight loss).
- Medicines containing tramadol (a pain-killer).
- 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).

Signs and symptoms of serotonin syndrome may include a combination of the following: restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea, vomiting. Get medical care right away if you think serotonin syndrome is happening to you.

The following medicines may also interact with Ranfaxine XL 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 Ranfaxisn XL with food and drink

Ranfaxisn XL should be taken with food.

You should avoid alcohol while you are taking Ranfaxisn XL.

Pregnancy and breast-feeding

Tell your doctor if you become pregnant, or you are trying to become pregnant. You should use Ranfaxisn XL only after discussing the potential benefits and the potential risks to your unborn child with your doctor.

If you are taking Ranfaxisn XL during pregnancy, let your doctor know, as your baby might have some symptoms when it is born. These symptoms usually begin during the first 24 hours after the baby is born. They include not feeding properly and trouble with breathing. If your baby has these symptoms when it is born and you are concerned, contact your doctor and/or midwife who will be able to advise you.

Venlafaxine passes into breast milk. There is a risk of an effect on the baby. Therefore, you should discuss the matter with your doctor, and he/she will decide whether you should stop breast-feeding or stop the therapy with Ranfaxisn XL.

Driving and using machines

Do not drive or use any tools or machines until you know how Ranfaxisn XL affects you.

3. HOW TO TAKE RANFAXINE XL

Always take Ranfaxisn XL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual recommended starting dose for treatment of depression is 75 mg per day. The dose can be raised by your doctor gradually, and if needed, even up to a maximum dose of 375 mg daily.

Take Ranfaxisn XL approximately the same time each day, either in the morning or in the evening. Capsules must be swallowed whole with fluid and not opened, crushed, chewed or dissolved.

Ranfaxisn XL should be taken with food.

If you have liver or kidney problems, talk to your doctor since your dose may need to be different.

Do not stop taking without talking to your doctor (see the section "If you stop taking Ranfaxisn XL").
If you take more Ranfaxine XL than you should
Call your doctor or pharmacist immediately if you take more than the amount of Ranfaxine XL prescribed by your doctor.

The symptoms of a possible overdose may include a rapid heart beat, changes in level of alertness (ranging from sleepiness to coma), blurred vision, seizures or fits, and vomiting.

If you forget to take Ranfaxine XL
If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take more than the daily amount of Ranfaxine XL that has been prescribed for you in one day.

If you stop taking Ranfaxine XL
Do not stop taking your treatment or reduce the dose without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Ranfaxine XL, he/she may ask you to reduce your dose slowly before stopping treatment altogether. Side effects are known to occur when people stop using Ranfaxine XL, especially when Ranfaxine XL is stopped suddenly or the dose is reduced too quickly. Some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, nausea, diarrhoea, nervousness, agitation, confusion, ringing in the ears, tingling or rarely electric shock sensations, weakness, sweating, seizures, or flu-like symptoms.

Your doctor will advise you on how you should gradually discontinue Ranfaxine XL treatment. If you experience any of these or other symptoms that are troublesome, ask your doctor for further advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ranfaxine XL 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 Ranfaxine XL. Inside Ranfaxine XL 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.

Allergic reactions
If any of the following happen, do not take more Ranfaxine XL. Tell your doctor immediately, or go to the casualty department at your nearest hospital:
- Chest tightness, wheezing, trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, dizziness, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious side effects
If you notice any signs of the following, you may need urgent medical attention:
- Heart problems, such as fast or irregular heart rate, increased blood pressure
- Eye problems, such as blurred vision, dilated pupils
- Nerve problems, such as dizziness, pins and needles, movement disorder, seizures or fits
- Psychiatric problems, such as hyperactivity and euphoria
- Treatment withdrawal (see the section “HOW TO TAKE RANFAXINE XL if you stop taking Ranfaxine XL”).

Complete side effect listing
The frequency (likelihood of occurring) of side effects is classified as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Affects more than 1 user in 10</td>
</tr>
<tr>
<td>Common</td>
<td>Affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare</td>
<td>Affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>Frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>
• Blood disorders
  Uncommon: bruising; black tarry stools (faeces) or blood in stools, which can be a sign of internal bleeding
  Not known: reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding; blood disorders which may lead to an increased risk of infection
• Metabolism/nutritional disorders
  Common: weight loss; increased cholesterol
  Uncommon: weight gain
  Not known: slight changes in blood levels of liver enzymes; decrease in blood sodium levels; itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis); confusion, excessive water intake (known as SIADH); abnormal breast milk production
• Nervous system disorders
  Very common: dry mouth; headache
  Common: abnormal dreams; decreased libido; dizziness; increased muscle tone; insomnia; nervousness; pins and needles; sedation; tremor; confusion; feeling separated (or detached) from yourself and reality
  Uncommon: lack of feeling or emotion; hallucinations; involuntary movement of the muscles; agitation; impaired coordination and balance
  Rare: a sensation of restlessness or an inability to sit or stand still; seizures or fits; feeling over-excited or euphoric
  Not known: a high temperature with rigid muscles, confusion or agitation, and sweating, or if you experience jerky muscle movements which you can't control, these may be symptoms of serious conditions known as neuroleptic malignant syndrome; euphoric feelings, drowsiness, sustained rapid eye movement, clumsiness, restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotoninergic syndrome; disorientation and confusion often accompanied by hallucination (delirium); stiffness, spasms and involuntary movements of the muscles; thoughts of harming or killing yourself
• Sight and hearing disorders
  Common: blurred vision
  Uncommon: altered taste sensation; ringing in the ears (tinnitus)
  Not known: severe eye pain and decreased or blurred vision
• Heart or circulation disorders
  Common: increase in blood pressure; flushing; palpitations
  Uncommon: feeling dizzy (particularly when standing up too quickly), fainting, fast heartbeat
  Not known: decrease in blood pressure; abnormal, rapid or irregular heart beat, which could lead to fainting
• Breathing disorders
  Common: yawning
  Not known: coughing, wheezing, shortness of breath and a high temperature, which are symptoms of inflammation of the lungs associated with an increase in white blood cells (pulmonary eosinophilia)
• Digestive disorders
  Very common: nausea
  Common: appetite decreased; constipation; vomiting
  Uncommon: grinding of the teeth; diarrhoea
  Not known: severe abdominal or back pains (which could indicate a serious problem in the gut, liver or pancreas)
• Skin disorders
  Very common: sweating (including night sweats)
  Uncommon: rash; abnormal hair loss
  Not known: skin rash, which may lead to severe blistering and peeling of the skin; itching; mild rash
• Muscle disorders
  Not known: unexplained muscle pain, tenderness or weakness (rhabdomyolysis)
• Urinary system disorders
  Common: difficulties passing urine; increased frequency in urination
  Uncommon: inability to pass urine
• Reproductive and sexual disorders
  Common: abnormal ejaculation/erectile dysfunction (impotence); menstrual irregularities such as increased bleeding or increased irregular bleeding
  Uncommon: abnormal orgasm (females)
- General
  Common: weakness (asthenia); chills
  Uncommon: sensitivity to sunlight
  Not known: swollen face or tongue, shortness of breath or difficulty breathing, often with skin rashes (this may be a serious allergic reaction)

  Ranfaxine XL sometimes causes unwanted effects that you may not be aware of, such as increases in blood pressure or abnormal heart beat; slight changes in blood levels or liver enzymes, sodium or cholesterol. More rarely, Ranfaxine XL may reduce the function of platelets in your blood, leading to an increased risk of bruising or bleeding. Therefore, your doctor may wish to do blood tests occasionally, particularly if you have been taking Ranfaxine XL for a long time.

  If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RANFAXINE XL

- Keep out of the reach and sight of children.
- Do not use Ranfaxine XL after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

  This medicinal product does not require any special storage conditions.

  Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help to protect the environment.

6. FURTHER INFORMATION

- What Ranfaxine XL contains
  Ranfaxine XL 37.5 mg prolonged release capsule, hard
  The active substance is venlafaxine.

  Each prolonged release capsule, hard contains 42.43 mg of Venlafaxine Hydrochloride equivalent to 37.5 mg of Venlafaxine.

  Other ingredients in these capsules are:
  - Core Spherical Composition: Cellulose, microcrystalline, Hypromellose,
  - Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

- Capsule Shell:
  - Body: Iron Oxide Red (E 172), Titanium Dioxide (E 171), Gelatin
  - Sodium Lauryl Sulfate
  - Cap: FD & C Blue 1 (E 133), D & C Yellow 10 (E 104), FD & C Red 40 (E 120), Titanium Dioxide (E 171), Gelatin
  - Sodium Lauryl Sulfate

  Ranfaxine XL 75 mg prolonged release capsule, hard
  The active substance is venlafaxine.

  Each prolonged release capsule, hard contains 84.85 mg of Venlafaxine Hydrochloride equivalent to 75 mg of Venlafaxine respectively.

  Other ingredients in these capsules are:
  - Core Spherical Composition: Cellulose, microcrystalline, Hypromellose,
  - Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

- Capsule Shell:
  - Body: Iron Oxide Red (E 172), Titanium Dioxide (E 171), Gelatin
  - Sodium Lauryl Sulfate
  - Cap: Iron Oxide Red (E 172), Titanium Dioxide (E 171), Gelatin
  - Sodium Lauryl Sulfate

  Ranfaxine XL 150 mg prolonged release capsules, hard
  The active substance is venlafaxine.

  Each prolonged release capsule, hard contains 169.71 mg of Venlafaxine Hydrochloride equivalent to 150 mg of Venlafaxine respectively.

  Other ingredients in these capsules are:
  - Core Spherical Composition: Cellulose, microcrystalline, Hypromellose,
  - Modified Release coating: Ethyl cellulose, Povidone (K 30), Triacetin and Talc

- Capsule Shell:
  - Body: Iron Oxide Red (E172), Iron Oxide Yellow (E172), Titanium Dioxide (E171), Gelatin
  - Sodium Lauryl Sulfate
  - Cap: Iron Oxide Red (E172), Iron Oxide Yellow (E172), Titanium Dioxide (E171), Gelatin
  - Sodium Lauryl Sulfate

- Black Printing Ink:
  - Shellac
  - Propylene glycol
  - Strong ammonia solution
  - Black iron oxide (E172)
  - Potassium hydroxide
What Ranfaxine XL looks like and contents of the pack

Ranfaxine XL is available in three strengths 37.5mg, 75mg and 150mg.
Each strength of Ranfaxine XL has a different marking/debossing on one side and is plain on the other side.
Ranfaxine XL 37.5 mg prolonged release capsule, hard
The 37.5 mg capsules are Size “2” capsule with grey opaque cap and pink opaque body imprinted with RVn on the cap and 37.5 on the body in black ink
The 37.5 mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 capsules are also available.
Not all pack sizes may be marketed
Ranfaxine XL 75 mg prolonged release capsule, hard
The 75 mg capsules are Size “1” capsule with pink opaque cap and body imprinted with RVn on the cap and 75 on the body in black ink
The 75 mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 capsules are also available.
Ranfaxine XL 150 mg prolonged release capsule, hard
The 150 mg capsules are Size “0” capsules with caramel opaque cap and body imprinted with RVn on the cap and 150 on the body in black ink.
The 150 mg capsules come in packs of 7, 10, 14, 20, 28, 30, 50, 56, 60, 100
For healthcare professionals, bottles of 100 capsules are also available.
Not all pack sizes may be marketed

Marketing Authorisation Holder:
Ranbaxy (UK) Limited
20 Balderston Street
London
W1K 6TL
United Kingdom

Manufacturer:
Ranbaxy Ireland Limited
Spafield, Cork Road,
Cashel, Co-Tipperary
Ireland

Cemelog – BRF Kft.
2040 Budaörs VasÚt u.2
Hungary

Terapia S.A.,
124 Fabrici Street,
Ciu-Napoca 400 632,
Romania

This medicinal product is authorized in the Member States of the EEA under the following names:
Belgium, The Netherlands- Venlaran
Ireland- Ranoflix XL
Poland- Venlafaxan
United Kingdom- Ranfaxine XL

This leaflet was last approved in October 2008

RANBAXY
Module 4

Labelling

PL 14894/0519

Blister:
Carton:

Each prolonged release capsules, hard contains 42.43 mg of venlafaxine hydrochloride equivalent to 37.5 mg venlafaxine

Oral use

Do not chew, displace, crush or place in water
Read the package leaflet before use
Keep out of the reach and sight of children.
Blister
Blister
Carton
MHRA PAR; RANFAXIRAN XL 37.5 MG, 75 MG AND 150 MG PROLONGED RELEASE CAPSULES, HARD
RANFAXINE XL 37.5 MG, 75 MG AND 150 MG PROLONGED RELEASE CAPSULES, HARD, PL 14894/0519-24
Blister
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Ranfaxiran XL and Ranfaxine XL 37.5mg, 75mg and 150mg prolonged release capsules, hard, in the treatment of major depressive episodes and for prevention of recurrence of major depressive episodes, is approvable.

EXECUTIVE SUMMARY

Problem statement
These abridged / hybrid applications are submitted under a combination of Articles 10(1) and 10(3) of Directive 2001/83/EC, as there is no 37.5 mg reference product in the UK.

The proposed products are claimed to be generic to the prolonged release formulations Efexor XL 75 mg (PL 00011/0223) and Efexor XL 150 mg (PL 00011/0224), that were authorised to Wyeth Laboratories in the UK on 5 August 1997.

With the UK as the Reference Member State in this Decentralised Procedure, Ranbaxy (UK) Limited applied for Marketing Authorisations for Ranfaxiran XL 37.5mg, 75mg and 150mg prolonged release capsules, hard in Belgium, Bulgaria, the Czech Republic, Ireland, Luxembourg, the Netherlands, Poland, Portugal, Romania and the Slovak Republic; the Ranfaxiran XL 75mg and 150mg tablet strengths in Austria, Germany, Denmark, Estonia, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Norway, Sweden and Slovenia; and Ranfaxine XL 37.5mg, 75mg and 150mg prolonged release capsules, hard in Belgium, Ireland, the Netherlands and Poland

About the product
The active ingredient venlafaxine hydrochloride has a well established clinical profile. It is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic or other available antidepressants. It is a racemate with two active enantiomers.

The proposed indications are for the treatment of major depressive episodes and for prevention of recurrence of major depressive episodes.

General comments on the submitted dossier
No new preclinical studies were submitted with this application. The GLP status of the studies described in the literature cannot be verified.

The bioequivalence studies submitted in support of these applications are all declared to be compliant with ICH-GCP.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as
certification that acceptable standards of GMP are in place at those sites.

For the finished product manufacturing site, which is located outside the Community, the RMS has accepted a copy of the current GMP certificates of satisfactory inspection summary reports issued by the inspection services of the competent authorities (MHRA) as certification that acceptable standards of GMP are in place at those non-Community sites.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Active substance**
The chemical-pharmaceutical documentation and Expert Report in relation to venlafaxine hydrochloride are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for active substance product are adequately drawn up.

Stability studies have been performed with the active substance. No significant changes in any parameters were observed. The proposed retest period of 24 months is justified.

**Finished Product**
The development of the product has been described, the choice of excipients is justified and their functions explained. The active ingredient and excipients used are well known and of pharmacopoeial quality.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on batches of each strength. The results are satisfactory.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for finished product are adequately drawn up.

The proposed shelf-life of 24 months with no special requirements for storage of the finished product is considered acceptable, as sufficient data has been provided.

**Non-clinical aspects**
The pharmacodynamic, pharmacokinetic and toxicological properties of venlafaxine are well known. As venlafaxine is a widely used, well-known active substance, no further studies are required and the applicant provides none. An overview based on a literature review is, thus, appropriate. The non-clinical overview presented on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

The preclinical toxicology of venlafaxine is well documented in the literature and no new data is supplied with the current applications. Clinical experience and the availability of human data supplant the need for further preclinical data.

The proposed limits for related substances comply with ICH Q3A(R2) - *Impurities in New Drug Substances* and ICHQ3B(R2) - *Impurities in New Drug Products*. The proposed residual solvent levels comply with ICH Q3C(R3) - *Impurities: Residual Solvents*.
From a preclinical point of view the text proposed for the SPC is acceptable as it is consistent with the UK reference product SPC.

Clinical aspects

To support the application the applicant has conducted three bioequivalence studies comparing the proposed product with the licensed UK brand leader product, Efexor XL (150mg capsules).

The company has studied the highest dose (150mg) of the three proposed for marketing. The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met. The studies performed on the 150mg strength are accepted as applicable to the 37.5mg and 75mg strengths.

Single dose fasted study
This was a comparative, randomised, two-way, two-period, single dose crossover study of conventional design in which 40 healthy fasted male volunteers were randomised to receive a single dose of 150mg orally of either the applicant's test product or the reference product. 90% Confidence Intervals for AUC0-t, AUC0-∞ and Cmax were all within conventional bioequivalence criteria for the parent drug and for O-desmethylvenlafaxine. The test and reference formulations can be considered to be bioequivalent in the fasted state.

Single dose fed study
This was a comparative, randomised, two-way, two-period, single dose crossover study in which volunteers received a single dose of 150mg orally of either the applicant's test product or the reference product after completing a standardised high-fat, high calorie breakfast. 90% Confidence Intervals for AUC0-t, AUC0-∞ and Cmax were all within conventional bioequivalence criteria and the test and reference formulations can be considered to be bioequivalent in the fed state.

Multiple dose fed study
This open-label, laboratory blind, multiple dose, randomised, two period cross-over study carried out in healthy male subjects. It consisted of two treatment phases each of five days, starting with a run-in period of 4 days (Days 1 to 4) during which subject received their randomised treatment every 24 hours, followed by a profile period of 24 hours (Day 5) and a drug-free washout period of 17 days between treatment phases.

The test and reference products met the standard criteria for bioequivalence at steady state for AUC, Cmax and Cmin for the parent drug and for O-desmethylvenlafaxine. The test and reference formulations can be considered to be bioequivalent at steady state.

Conclusions
Bioequivalence to the licensed UK brand leader product, Efexor XL, has been demonstrated according to the standard requirements for oral prolonged release products.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the
notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**
The RMS considers that the proposed pharmacovigilance activities and risk minimisation activities are satisfactory.

**Periodic Safety Update Report (PSUR)**
The applicant has applied for a PSUR submission scheme of 3 years upon approval as venlafaxine is a well known active substance which has been marketed for many years throughout the EU and the PSUR cycle will follow that of the brand leader innovator product.

**BENEFIT RISK ASSESSMENT**
Bioequivalence has been shown and a positive risk-benefit has been established.
Overall conclusion

QUALITY
The important quality characteristics of Ranfaxiran XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard and Ranfaxine XL 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard are well defined and controlled. The specification and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No preclinical data is needed for this application.

No new or unexpected safety concerns arise from this application.

EFFICACY
Previous clinical studies have demonstrated the efficacy of venlafaxine hydrochloride in the treatment of prostate cancer.

The product literature is satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.