Public Assessment Report

Decentralised Procedure

Venlafaxine 25 / 37.5 / 50 / 75 mg Tablets
Ranoven 37.5 and 75mg Tablets
(Venlafaxine Hydrochloride)

UK/H/974/01-04/DC
UK/H/975/01-02/DC

UK Licence Number: PL 14894/0473-6 and
PL 14894/0477-8

Ranbaxy UK Limited
LAY SUMMARY

The MHRA granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Venlafaxine 25, 37.5, 50, and 75mg Tablets and Ranoven 37.5mg and 75mg Tablets. These are prescription-only medicines (POM) that are used to treat the symptoms of depressive illness including depression accompanied by anxiety.

Venlafaxine hydrochloride is an antidepressant drug belongs to the class of medicines called Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Venlafaxine/Ranoven Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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Module 1

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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25mg venlafaxine (equivalent to 28.275mg of venlafaxine hydrochloride).
For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Venlafaxine 25mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘1’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Major depressive disorder
Venlafaxine 25mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety.
Following an initial response Venlafaxine 25mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Venlafaxine 25mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Venlafaxine Tablets be taken with food and sufficient fluid at the same time of day.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements. The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).
Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.

Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.
Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment.
The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary.
For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Venlafaxine 25mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered. Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

Elderly Patients:
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

Children/Adolescents:
Venlafaxine 25mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years.

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Venlafaxine 25mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects).

The efficacy and safety of Venlafaxine 25mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

Maintenance/Continuation/Extended Treatment:
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine 25mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine 25mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment.

Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

Withdrawal symptoms seen on discontinuation of venlafaxine
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

4.3 Contraindications
1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with Other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

4.4 Special warnings and precautions for use
1. Suicide/suicidal thoughts. 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 self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose. 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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal 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 advisable that venlafaxine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 25mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency. Venlafaxine 25mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.
14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

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

Venlafaxine 25mg Tablets 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.

22. Use in Elderly

Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants. Particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.

4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Venlafaxine 25mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine 25mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

**Lithium:** Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

**Imipramine/desipramine:** The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and Cmax were increased by approximately 35%.
**Haloperidol:** In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in C\text{max} for haloperidol. The elimination half-life remained unchanged.

**Diazepam:** The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.

**Clozapine:** Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

**Alcohol:** Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Venlafaxine 25mg Tablets.

**ECT:** There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

**Drugs metabolised by Cytochrome P450 isoenzymes:** The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

**Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450:** Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

**Cimetidine:** Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Venlafaxine 25mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Venlafaxine 25mg Tablets are administered with cimetidine.

**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 ODV. The clinical significance of this interaction is not known.

**Anticoagulants:** Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirinsalicyclic acid derivatives, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.

**St. John’s wort (Hypericum perforatum):** The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

**Risperidone:** During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

### 4.6 Pregnancy and lactation

There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Venlafaxine 25mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

### 4.7 Effects on ability to drive and use machines

Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.
4.8 Undesirable effects

See also Special Warnings and Special Precautions for Use. The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthena and abnormal ejaculation/orgasm.

The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common (<1/10 and >1/100); uncommon (<1/1000 and >1/1000); rare (<1/10000); very rare (<1/100000);

**Blood and lymphatic system disorders** - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

**Cardiovascular and vascular disorders** (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsades de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

**Gastrointestinal disorders** - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

**General disorders** - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis.

**Metabolic and nutritional disorders** - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes**; Very rare: hepatitis; Very rare: prolactin increased.

**Musculo-skeletal disorders** - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

**Neurological disorders** - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), increased liver enzymes** (see below); Rare: hepatitis; Very rare: prolactin increased.

**Respiratory system disorders** - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

**Skin and subcutaneous tissue disorders** - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

**Special senses** - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

**Adverse events from paediatric clinical trials**

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

**Withdrawal symptoms seen on discontinuation of venlafaxine treatment**

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

**Special Notes:**
* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Venlafaxine 25mg Tablets are usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.
** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

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

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antidepressants
ATC code: N06AX16
Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

5.2 Pharmacokinetic properties
Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.
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.
Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients
Lactose, anhydrous
Sodium starch glycolate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Magnesium stearate

Extragranular ingredients
Cellulose, microcrystalline
Sodium starch glycollate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Purified talc
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C. Store in the original package.

6.5 Nature and contents of container
PVC/aluminium foil blisters (pack size 28, 30, 42, 56, 60, 100 tablets)
or
PVC/ACLAR/aluminium foil blisters (pack size 28, 30, 42, 56, 60, 100 tablets)
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited.
20 Balderton Street,
London
W1k 6TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0473

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/02/2008

10 DATE OF REVISION OF THE TEXT
15/02/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 37.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 37.5mg venlafaxine (equivalent to 42.413mg of venlafaxine hydrochloride). For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Venlafaxine 37.5mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘2’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Major depressive disorder
Venlafaxine 37.5mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety.
Following an initial response Venlafaxine 37.5mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Venlafaxine 37.5mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Venlafaxine Tablets be taken with food and sufficient fluid at the same time of day.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements. The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).

Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.

Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.

Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment.
The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary.
For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Venlafaxine 37.5mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered.

Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

Elderly Patients:
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

Children/Adolescents:
Venlafaxine 37.5mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years.

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Venlafaxine 37.5mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects).

The efficacy and safety of Venlafaxine 37.5mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

Maintenance/Continuation/Extended Treatment:
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine 37.5mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine 37.5mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment.

Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

Withdrawal symptoms seen on discontinuation of venlafaxine
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

4.3 Contraindications
1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

4.4 Special warnings and precautions for use
1. Suicide/suicidal thoughts. 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 self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal 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 "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 37.5mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency. Venlafaxine 37.5mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of
drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

21. Use in children and adolescents under 18 years of age
Venlafaxine 37.5mg Tablets 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.

22. Use in Elderly
Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants. Particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.
4.5 Interaction with other medicinal products and other forms of interaction

MAOIs: The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Venlafaxine 37.5mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine 37.5mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

Lithium: Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

Imipramine/desipramine: The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and \( C_{\text{max}} \) were increased by approximately 35%.

Haloperidol: In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in \( C_{\text{max}} \) for haloperidol. The elimination half-life remained unchanged.

Diazepam: The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.

Clozapine: Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

Alcohol: Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Venlafaxine 37.5mg Tablets.

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Venlafaxine 37.5mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Venlafaxine 37.5mg Tablets are administered with cimetidine.

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 ODV. The clinical significance of this interaction is not known.

Anticoagulants: Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirin, salicylic acid derivatives, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.
**St. John’s wort (Hypericum perforatum):** The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

**Risperidone:** During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

4.6 Pregnancy and lactation
There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown.

Venlafaxine 37.5mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on ability to drive and use machines
Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects
See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm.

The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common ( <1/10 and >1/100); uncommon (<1/100 and >1/1000); rare (<1/1000); very rare (<1/10,000): Blood and lymphatic system disorders - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypotension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

Gastrointestinal disorders - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

General disorders - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis

Metabolic and nutritional disorders - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes** (see below); Rare: hepatitis; Very rare: prolactin increased.

Musculo-skeletal disorders - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

Neurological disorders - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), serotoninergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

Renal and urinary disorders - Common: urinary frequency; Uncommon: urinary retention.
Reproductive and breast disorders - Very common: anorgasmia, erectile dysfunction, abnormal ejaculation/orgasm; Common: decreased libido, impotence, menstrual cycle disorders; Uncommon: menorrhagia; Rare: galactorrhoea.

Respiratory system disorders - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

Skin and subcutaneous tissue disorders - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

Special senses - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

**Adverse events from paediatric clinical trials**

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

**Special Notes:**

* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Venlafaxine 37.5mg Tablets are usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.

** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

### 4.9 Overdose

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

The haemodialysis clearance of venlafaxine and its main active metabolite, are low. Therefore, they are not considered dialysable. Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants ATC code: N06AX16

Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.
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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake. Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors in vitro. Pharmacologic activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular effects.

5.2 Pharmacokinetic properties
Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

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. Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Intragranular ingredients
Lactose, anhydrous
Sodium starch glycolate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Magnesium stearate

Extragranular ingredients
Cellulose, microcrystalline
Sodium starch glycollate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Purified talc
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25ºC. Store in the original package.

6.5 Nature and contents of container
PVC/aluminium foil blisters (pack size 28, 30, 56, 60 tablets)
or
PVC/ACLAR/aluminium foil blisters (pack size 28, 30, 56, 60 tablets)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited.
20 Balderton Street,
London
W1k 6TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0474

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/02/2008

10 DATE OF REVISION OF THE TEXT
15/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50mg of venlafaxine (equivalent to 56.550mg of venlafaxine hydrochloride). For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Venlafaxine 50mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘3’ on either side of breakline and breakline on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Major depressive disorder
Venlafaxine 50mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety. Following an initial response Venlafaxine 50mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Venlafaxine 50mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).
Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Venlafaxine Tablets be taken with food and sufficient fluid at the same time of day. If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements. The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4). Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.
Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.

Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment. The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary. For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Venlafaxine 50mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered.
Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

**Elderly Patients:**
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

**Children/Adolescents:**
Venlafaxine 50mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years.
Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Venlafaxine 50mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects). The efficacy and safety of Venlafaxine 50mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine 50mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine 50mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment.
Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

**Withdrawal symptoms seen on discontinuation of venlafaxine**
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

**4.3 Contra-indications**
1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

**4.4 Special warnings and precautions for use**
1. **Suicide/suicidal thoughts.** 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 self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose.
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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal 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 "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 50mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency. Venlafaxine 50mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.
15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

21. Use in children and adolescents under 18 years of age
Venlafaxine 50mg Tablets 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.

22. Use in Elderly
Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants. Particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.

4.5 Interaction with other medicinal products and other forms of interaction

MAOIs: The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Venlafaxine 50mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine 50mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

Lithium: Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

Imipramine/desipramine: The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and Cmax were increased by approximately 35%.

Haloperidol: In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in Cmax for haloperidol. The elimination half-life remained unchanged.
Diazepam: The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.

Clozapine: Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

Alcohol: Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Venlafaxine 50mg Tablets.

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRIs antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Venlafaxine 50mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Venlafaxine 50mg Tablets are administered with cimetidine.

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

Anticoagulants: Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirinsalicylic acid derivates, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.

St. John’s wort (Hypericum perforatum): The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

Risperidone: During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

4.6 Pregnancy and lactation
There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Venlafaxine 50mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on ability to drive and use machines
Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.
4.8 Undesirable effects

See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm.

The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common ( <1/10 and>1/100); uncommon (<1/100 and<1/1000); rare (<1/1000);very rare (<1/10,000).

Blood and lymphatic system disorders - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

Gastrointestinal disorders - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

General disorders - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis

Metabolic and nutritional disorders - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes** (see below); Rare: hepatitis; Very rare: prolactin increased.

Musculo-skeletal disorders - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

Neurological disorders - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and coordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

Renal and urinary disorders - Common: urinary frequency; Uncommon: urinary retention.

Reproductive and breast disorders - Very common: anorgasmia, erectile dysfunction, abnormal ejaculation/orgasm; Common: decreased libido, impotence, menstrual cycle disorders; Uncommon: menorrhagia; Rare: galactorrhoea.

Respiratory system disorders - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

Skin and subcutaneous tissue disorders - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

Special senses - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

Adverse events from paediatric clinical trials

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

**Special Notes:**
* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Venlafaxine 50mg Tablets are usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.
** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

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

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Other antidepressants ATC code: N06AX16
Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

**5.2 Pharmacokinetic properties**
Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.
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. Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Intragranular ingredients**
Lactose, anhydrous
Sodium starch glycolate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Magnesium stearate

**Extragranular ingredients**
Cellulose, microcrystalline
Sodium starch glycollate
Yellow ferric oxide (E172)
Red ferric oxide (E172)
Purified talc
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C. Store in the original package.

6.5 Nature and contents of container
PVC/aluminium foil blisters (pack size 30, 42, 60 tablets)
or
PVC/ACLAR/aluminium foil blisters (pack size 30, 42, 60 tablets)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0475

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/02/2008

10 DATE OF REVISION OF THE TEXT
15/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 75mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 75mg venlafaxine (equivalent to 84.825 mg of venlafaxine hydrochloride).
For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Venlafaxine 75mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘4’ on either side of breakline and breakline on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Major depressive disorder
Venlafaxine 75mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety.
Following an initial response Venlafaxine 75mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Venlafaxine 75mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).
Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Venlafaxine Tablets be taken with food and sufficient fluid at the same time of day.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements.
The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).
Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.
Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.
Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment.
The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary. For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Venlafaxine 75mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered.
Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

**Elderly Patients:**
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

**Children/Adolescents:**
Venlafaxine 75mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Venlafaxine 75mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects).

The efficacy and safety of Venlafaxine 75mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine 75mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine 75mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment. Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

**Withdrawal symptoms seen on discontinuation of venlafaxine**
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

### 4.3 Contraindications
1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

### 4.4 Special warnings and precautions for use
1. Suicide/suicidal thoughts. 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 self-harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal 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 "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 75mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency Venlafaxine 75mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.
15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

21. Use in children and adolescents under 18 years of age
Venlafaxine 75mg Tablets 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.

22. Use in Elderly
Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants. Particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.

4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Venlafaxine 75mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine 75mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

**Serotonergic drugs:** Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

**Lithium:** Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

**Imipramine/desipramine:** The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and Cmax were increased by approximately 35%.

**Haloperidol:** In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in Cmax for haloperidol. The elimination half-life remained unchanged.

**Diazepam:** The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.
Clozapine: Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

Alcohol: Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Venlafaxine 75mg Tablets.

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Venlafaxine 75mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Venlafaxine 75mg Tablets are administered with cimetidine.

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

Anticoagulants: Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirin-salicylic acid derivates, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.

St. John’s wort (Hypericum perforatum): The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

Risperidone: During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

4.6 Pregnancy and lactation

There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Venlafaxine 75mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on ability to drive and use machines

Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm.
The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common ( <1/10 and>1/100); uncommon (<1/100 and>1/1000); rare ( <1/1000); very rare ( <1/10,000);

Blood and lymphatic system disorders - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

Gastrointestinal disorders - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

General disorders - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis.

Metabolic and nutritional disorders - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes* (see below); Rare: hepatitis; Very rare: prolactin increased.

Musculo-skeletal disorders - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

Neurological disorders - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and coordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

Renal and urinary disorders - Common: urinary frequency; Uncommon: urinary retention.

Reproductive and breast disorders - Very common: anorgasmia, erectile dysfunction, abnormal ejaculation/orgasm; Common: decreased libido, impotence, menstrual cycle disorders; Uncommon: menorrhagia; Rare: galactorrhoea.

Respiratory system disorders - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

Skin and subcutaneous tissue disorders - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

Special senses - Common: abnormal vision/accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

Adverse events from paediatric clinical trials

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

Special Notes:

* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Venlafaxine 75mg Tablets are usually mild to moderate, and
infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.

** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

4.9 Overdose

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

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

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants        ATC code: N06AX16

Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

5.2 Pharmacokinetic properties

Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

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. Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Intrgranular ingredients**
- Lactose, anhydrous
- Sodium starch glycolate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Magnesium stearate

**Extragranular ingredients**
- Cellulose, microcrystalline
- Sodium starch glycollate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Purified talc
- Silica, colloidal anhydrous
- Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25ºC. Store in the original package.

6.5 Nature and contents of container
PVC/aluminium foil blisters (pack size 14, 30, 56, 60 tablets)
or
PVC/ACLAR/aluminium foil blisters (pack size 14, 30, 56, 60 tablets)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0476

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/02/2008

10 DATE OF REVISION OF THE TEXT
15/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Ranoven 37.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 37.5mg venlafaxine (equivalent to 42.413mg of venlafaxine hydrochloride). For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Ranoven 37.5mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘2’ on one side and plain on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Major depressive disorder
Ranoven 37.5mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety. Following an initial response Ranoven 37.5mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Ranoven 37.5mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).
Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Ranoven Tablets be taken with food and sufficient fluid at the same time of day.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements. The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).
Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.
Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.
Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment.
The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary.
For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Ranoven 37.5mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered.
Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

**Elderly Patients:**
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

**Children/Adolescents:**
Ranoven 37.5mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years.

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Ranoven 37.5mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects).

The efficacy and safety of Ranoven 37.5mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Ranoven 37.5mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Ranoven 37.5mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment.

Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

**Withdrawal symptoms seen on discontinuation of venlafaxine**
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

### 4.3 Contraindications

1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

### 4.4 Special warnings and precautions for use

1. Suicide/suicidal thoughts. 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 self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhea, palpitations and emotional instability are the most commonly reported withdrawal 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 "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Ranoven 37.5mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency Ranoven 37.5mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.
15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

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

Ranoven 37.5mg Tablets 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.

22. Use in Elderly

Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants, particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.

4.5 Interaction with other medicinal products and other forms of interaction

MAOIs: The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Ranoven 37.5mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Ranoven 37.5mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

Lithium: Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

Imipramine/desipramine: The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and Cmax were increased by approximately 35%.

Haloperidol: In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in Cmax for haloperidol. The elimination half-life remained unchanged.

Diazepam: The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.
Clozapine: Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

Alcohol: Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Ranoven 37.5mg Tablets.

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Ranoven 37.5mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Ranoven 37.5mg Tablets are administered with cimetidine.

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

Anticoagulants: Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirin, salicylic acid derivatives, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.

St. John’s wort (Hypericum perforatum): The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

Risperidone: During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

4.6 Pregnancy and lactation

There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Ranoven 37.5mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on ability to drive and use machines

Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthma and abnormal ejaculation/orgasm.
The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common ( <1/10 and>1/100); uncommon (<1/100 and>1/1000); rare ( <1/1000); very rare ( <1/10,000):

**Blood and lymphatic system disorders** - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

**Cardiovascular and vascular disorders** (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

**Gastrointestinal disorders** - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

**General disorders** - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis.

**Metabolic and nutritional disorders** - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes** (see below); Rare: hepatitis; Very rare: prolactin increased.

**Musculo-skeletal disorders** - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

**Neurological disorders** - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

**Respiratory system disorders** - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

**Skin and subcutaneous tissue disorders** - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

**Special senses** - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

**Adverse events from paediatric clinical trials**

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

**Withdrawal symptoms seen on discontinuation of venlafaxine treatment**

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).
**Special Notes:**

* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Ranoven 37.5mg Tablets are usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.

** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

### 4.9 Overdose

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs). The haemodialysis clearance of venlafaxine and its main active metabolite, are low. Therefore, they are not considered dialysable.

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Other antidepressants  
**ATC code:** N06AX16

Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers. 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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake. Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors in vitro. Pharmacologic activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular effects.

#### 5.2 Pharmacokinetic properties

Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

#### 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.
Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients
- Lactose, anhydrous
- Sodium starch glycolate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Magnesium stearate

Extragranular ingredients
- Cellulose, microcrystalline
- Sodium starch glycinate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Purified talc
- Silica, colloidal anhydrous
- Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C. Store in the original package.

6.5 Nature and contents of container
- PVC/aluminium foil blisters (pack size 56 tablets)
- or
- PVC/ACLAR/aluminium foil blisters (pack size 56 tablets)

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0477

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/02/2008

10 DATE OF REVISION OF THE TEXT
19/02/2008
1 NAME OF THE MEDICINAL PRODUCT
Ranoven 75mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 75mg venlafaxine (equivalent to 84.825 mg of venlafaxine hydrochloride). For a full list of excipients, see section 6.1. Each tablet also contains lactose anhydrous.

3 PHARMACEUTICAL FORM
Tablet
Ranoven 75mg Tablets are peach coloured, mottled, uncoated, shield shaped tablets debossed with ‘V’ and ‘4’ on either side of breakline and breakline on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Major depressive disorder
Ranoven 75mg Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety. Following an initial response Ranoven 75mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4.2 Posology and method of administration
Treatment with Ranoven 75mg Tablets should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).
Depression:
The recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that Ranoven Tablets be taken with food and sufficient fluid at the same time of day.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.
In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed or hospitalised patients who require daily doses of 300 mg or more, treatment should be initiated under specialist supervision including shared care arrangements. The maximum recommended dose is 375mg per day.
The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).
Usually, the dosage for prevention of relapse or for prevention of recurrence of a new episode is similar to that used during the index episode. Patients should be re-assessed regularly in order to evaluate the benefit of long-term therapy.
Patients at increased risk for suicide (see also sections 4.4 and 4.9):
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide related behaviour (see section 4.4 and 4.9) and a limited number of tablets should be provided to reduce the risk from overdose. A maximum of two weeks supply should be considered in these patients at initiation of treatment, during any dosage adjustment and until improvement occurs.
Patients with Renal or Hepatic Impairment:
Lower venlafaxine doses should be given to patients with renal or hepatic impairment.
The total dose must be reduced by 25-50% in renal impaired patients with a glomerular filtration rate of 10 to 70 ml/min. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
For patients with mild hepatic impairment (PT <14 seconds), no change in dosage is necessary. For patients with moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to the longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.
Insufficient data are available to support the use of Ranoven 75mg Tablets in patients with severe renal impairment (GFR <10ml/minute) or severe hepatic impairment (PT>18 seconds). In patients with severe hepatic impairment (PT>18 seconds) venlafaxine may be used with caution and a dose reduction by more than 50% should be considered.
Venlafaxine is not suitable for patients receiving haemodialysis. Administration should be postponed until the dialysis session is completed.

**Elderly Patients:**
No adjustment in the usual dosage is recommended for elderly patients. However, as with any therapy, caution should be exercised in treating the elderly (e.g. due to the possibility of renal impairment. See also dosage recommendations for renal impairment). The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

**Children/Adolescents:**
Ranoven 75mg Tablets should not be used in the treatment of children and adolescents under the age of 18 years.
Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of Ranoven 75mg Tablets in these patients (see sections 4.3 Contra-indications and 4.8 Undesirable Effects). The efficacy and safety of Ranoven 75mg Tablets for other indications in children and adolescents under the age of 18 have not yet been established.

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Ranoven 75mg Tablets for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Ranoven 75mg Tablets have been shown to be efficacious during long-term (up to 12 months) treatment.
Venlafaxine has been shown to be effective for preventing relapse, or recurrence of new episodes, in patients responding to venlafaxine treatment during the index episode.

**Withdrawal symptoms seen on discontinuation of venlafaxine**
Abrupt discontinuation should be avoided (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. 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.

### 4.3 Contraindications
1. Known hypersensitivity to venlafaxine or any other component of the product.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors (See Interactions with other Medicaments and Other Forms of Interactions).
3. Venlafaxine should not be used in patients with an identified very high risk of a serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension (see section 4.4).
4. Closed-angle glaucoma
5. Micturition disorders as a result of an obstruction of urinary flow e.g. prostate disease

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

### 4.4 Special warnings and precautions for use
1. Suicide/suicidal thoughts. 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 self harm is highest shortly after presentation and the risk of suicide may increase again in the early stages of recovery. Furthermore, there is evidence that in children and adolescents, antidepressants may increase the risk of suicidal thoughts and self-harm. Consequently, treatment should be commenced at the lowest possible dose in order to minimise the risk of an overdose.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 paresthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhea, palpitations and emotional instability are the most commonly reported withdrawal 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 "Withdrawal Symptoms Seen on Discontinuation of Venlafaxine", Section 4.2 Posology and Method of Administration).

3. Activation of mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, venlafaxine should be used with caution in patients with a history of mania.

4. Treatment with venlafaxine (especially starting and discontinuing treatment) has been associated with reports of aggression. Therefore venlafaxine should be used with caution in patients with a history of aggressive behaviour.

5. Psychomotor restlessness: The use of venlafaxine has been associated with the development of psychomotor restlessness, which clinically may be very similar to 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 and it may be necessary to review the use of venlafaxine.

6. Patients with cardiac disease. Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction) (see also sections 4.3 and 4.8). People with a recent history of myocardial infarction or unstable heart disease were excluded from all clinical trials. However, patients with other pre-existing heart disease were not excluded, although they were neither separately analysed nor systematically evaluated. Venlafaxine should be used with caution in patients with cardiac arrhythmia or hypertension.

7. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine.

8. Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine (see section 4.3). Cases of elevated blood pressure requiring immediate treatment have been reported.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Ranoven 75mg Tablets should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure or if there is an increase in seizure frequency Ranoven 75mg Tablets should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.8).

10. Due to the possibility of drug abuse with CNS-active drugs, physicians should evaluate patients for a history of drug abuse, and follow such patients closely. Clinical studies have shown no evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking venlafaxine.

11. Increases in heart rate can occur, particularly at high doses. The mean heart rate has been reported to increase by approximately 4 beats/minute in patients treated with venlafaxine. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate.

12. Dosage should be reduced in patients with moderate-severe renal impairment or hepatic cirrhosis (see sections 4.2 and 4.5).

13. Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.

14. Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.
15. Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at a risk of narrow angle glaucoma should be monitored closely.

16. There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptake inhibitors (SSRIs). Other bleeding manifestations (e.g. gastrointestinal bleeding and mucous membrane bleeding) have been reported. Caution is advised in patients predisposed to bleeding due to factors such as age, underlying medical conditions or concomitant medications.

17. 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 has been reported. Measurement of serum cholesterol levels should be considered during long-term treatment.

18. 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.

19. As with SSRIs, venlafaxine should be used with caution in patients already receiving neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination.

20. Serotonin syndrome has been rarely reported in association with concomitant use with SSRIs. Therefore venlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

21. Use in children and adolescents under 18 years of age
Ranoven 75mg Tablets 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.

22. Use in Elderly
Caution should be exercised when venlafaxine is used in the elderly, particularly if such patients are using diuretics, or if they are otherwise suffering from volume depletion. Since elderly patients are often more sensitive to antidepressants. Particular cautions should be exercised when increasing the dosage (see section 4.2).

23. Venlafaxine should be used with caution in patients with prostatic hypertrophy and other stenosis conditions of gastrointestinal and genitourinary apparatus.

4.5 Interaction with other medicinal products and other forms of interaction

MAOIs: The combined administration of Venlafaxine and MAOI is contraindicated (see section 4.4). Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Ranoven 75mg Tablets in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Ranoven 75mg Tablets before starting an MAOI (see also Contra-indications).

In the case of reversible MAOI (e.g. moclobemide), the period between treatments can be reduced to less than 14 days. However, the pharmacological properties of the substances and the clinical findings of the patients must be taken into consideration.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, caution is advised when venlafaxine is co-administered with drugs that may affect the serotonergic neurotransmitter systems (such as triptans, SSRIs or lithium). (see section 4.4)

Lithium: Reports have been received of an interaction between lithium and venlafaxine leading to increased lithium levels.

Imipramine/desipramine: The metabolism of imipramine and its metabolite 2-OH-imipramine were unaffected by venlafaxine although the total renal clearance of 2-hydroxydesipramine was reduced and desipramine AUC and Cmax were increased by approximately 35%.

Haloperidol: In a pharmacokinetic study co-administration of venlafaxine with a single 2mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in Cmax for haloperidol. The elimination half-life remained unchanged.

Diazepam: The pharmacokinetic profiles of venlafaxine and ODV were not significantly altered by the administration of diazepam. Venlafaxine has no effect on the pharmacokinetic profile of diazepam or on the psychomotor or psychometric effects induced by diazepam.
PAR Venlafaxine 25, 37.5, 50 and 75mg Tablet

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Clozapine: Increased levels of clozapine, that were temporarily associated with adverse events, including seizures, have been reported following the addition of venlafaxine.

Alcohol: Venlafaxine has been shown not to increase the impairment of mental or motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Ranoven 75mg Tablets.

ECT: There is little clinical experience of the concurrent use of venlafaxine with ECT. As prolonged seizure activity has been reported with concomitant SSRI antidepressants, caution is advised.

Drugs metabolised by Cytochrome P450 isoenzymes: The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Venlafaxine is primarily metabolised to its active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. Although CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, there is potential for a clinically significant drug interaction between inhibitors of CYP3A4 mediated metabolism and venlafaxine as this could result in increased venlafaxine plasma levels in poor CYP2D6 metabolizers. Therefore, potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine if strictly indicated.

Effect of venlafaxine on the metabolism of other drugs metabolised by cytochrome P450: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4. This was confirmed by in vivo studies with the following drugs: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4) and diazepam (CYP3A4 and CYP2C19).

Cimetidine: Cimetidine inhibited the first-pass metabolism of venlafaxine but had no significant effect on the formation or elimination of ODV, which is present in much greater quantities in the systemic circulation. No dosage adjustment therefore seems necessary when Ranoven 75mg Tablets are co-administered with cimetidine. For elderly patients, or patients with hepatic dysfunction the interaction could potentially be more pronounced, and for such patients clinical monitoring is indicated when Ranoven 75mg Tablets are administered with cimetidine.

Indinavir: A pharmacokinetic study with indinavir has shown a 28% decrease in AUC and a 36% decrease in C_max for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this interaction is not known.

Anticoagulants: Caution should be exercised during concomitant use of selective serotonin reuptake inhibitors (SSRIs) with anticoagulants (warfarin, heparin etc.), antiplatelet drugs (e.g. NSAIDs, aspirin/salicylic acid derivatives, ticlopidin etc.) or other medicinal products that may increase the risk of bleeding. Caution should be used with patients with coagulation disorders. Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin, following the addition of venlafaxine.

St. John’s wort (Hypericum perforatum): The concomitant use of venlafaxine with products containing St. John’s wort (Hypericum perforatum) may lead to potentiation of serotonergic activity with greater incidence of adverse events.

Risperidone: During concomitant use of venlafaxine and risperidone, venlafaxine increased the AUC (+32%) of risperidone while the pharmacokinetic profile of 9-hydroxyrisperidone and the active moiety (risperidone and 9-OH-risperidone) was not significantly changed.

4.6 Pregnancy and lactation

There are no adequate data from the use of venlafaxine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Ranoven 75mg Tablets should not be used during pregnancy unless clearly necessary. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

There is evidence to suggest that venlafaxine and its metabolite, ODV, transfers into breast milk. Therefore, a decision should be made whether or not to breast-feed or to discontinue venlafaxine.

4.7 Effects on ability to drive and use machines

Although venlafaxine has been shown not to affect psychomotor, cognitive, or complex behaviour performance in healthy volunteers, any psychoactive drug may impair judgement, thinking or motor skills. Therefore patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects

See also Special Warnings and Special Precautions for Use.

The most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo were: nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm.
The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

Adverse events observed with venlafaxine, from both spontaneous and clinical trials reports, are classified in body systems and listed below as very common (>1/10); common ( <1/10 and>1/100); uncommon (<1/100 and>1/1000); rare ( <1/1000); very rare ( <1/10,000):

**Blood and lymphatic system disorders** - Uncommon: ecchymosis, mucous membrane bleeding, bleeding of small areas of skin; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

**Cardiovascular and vascular disorders** (see Special Warnings and Special Precautions for Use) - Common: increase in blood pressure, hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, atrial and ventricular fibrillation.

**Gastrointestinal disorders** - Very common: constipation, nausea* (see below); Common: anorexia, appetite decreased, diarrhoea, dyspepsia, vomiting; Uncommon: bruxism; Rare: gastrointestinal bleeding; Very rare: pancreatitis.

**General disorders** - Very common: asthenia, headache; Common: abdominal pain, chills, pyrexia; Rare: anaphylaxis.

**Metabolic and nutritional disorders** - Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see Special Warnings and Special Precautions for Use), weight gain or loss; Uncommon: hyponatraemia including SIADH (see Special Warnings and Special Precautions for Use), increased liver enzymes** (see below); Rare: hepatitis; Very rare: prolactin increased.

**Musculo-skeletal disorders** - Common: arthralgia, increased muscle tension, myalgia; Uncommon: muscle spasm; Very rare: rhabdomyolysis.

**Neurological disorders** - Very common: dizziness, dry mouth, insomnia, nervousness, sedation, somnolence; Common: abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; Uncommon: apathy, hallucinations, myoclonus; Rare: ataxia and disorders of balance and coordination, speech disorders including dysarthria, mania or hypomania (see Special Warnings and Special Precautions for Use), neuroleptic malignant syndrome-like effects, seizures (see below and Special Warnings and Special Precautions for Use), serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use).

**Reproductive and breast disorders** - Very common: anorgasmia, erectile dysfunction, abnormal ejaculation/orgasm; Common: decreased libido, impotence, menstrual cycle disorders; Uncommon: menorrhagia; Rare: galactorrhoea.

**Respiratory system disorders** - Common: dyspnoea, yawning; Very rare: pulmonary eosinophilia.

**Skin and subcutaneous tissue disorders** - Very common: sweating (including night sweats); Common: pruritus, rash; Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia; Rare: itching, erythema multiforme, Stevens Johnson syndrome.

**Special senses** - Common: abnormal vision/ accommodation, mydriasis, tinnitus; Uncommon: altered taste sensation; Rare: closed-angle glaucoma.

**Adverse events from paediatric clinical trials**

In paediatric MDD clinical trials the following adverse events were reported at a frequency of at least 2% of patients and occurred at a rate of at least twice that of placebo: abdominal pain, chest pain, tachycardia, anorexia, weight loss, constipation, dyspepsia, nausea, ecchymosis, epistaxis, mydriasis, myalgia, dizziness, emotional lability, tremor, hostility and suicidal ideation.

**Withdrawal symptoms seen on discontinuation of venlafaxine treatment**

Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convolution, vertigo, tinnitus, dry mouth and anorexia. 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 section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).
Special Notes:
* Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Ranoven 75mg Tablets are usually mild to moderate, and infrequently results in vomiting or withdrawal. The incidence increases with higher doses particularly when the dose is increased rapidly.
** Reversible increases in liver enzymes are seen in a small number of patients treated with venlafaxine. These generally resolve on discontinuation of therapy.

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

Management of Overdosage - Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended, as are general supportive and symptomatic measures. Use of activated charcoal or gastric lavage should be considered. Induction of emesis is not recommended. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement (e.g. concomitant intake with SSRIs or other psychotropic drugs).

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

Retrospective analyses from the United Kingdom (UK) report the rate of antidepressant overdose deaths per million prescriptions. In these analyses, the rate for venlafaxine is higher than that for SSRIs, but lower than that for tricyclic antidepressants. These analyses did not adjust for suicide risk factors. An epidemiological study in patients prescribed antidepressants in the UK showed that venlafaxine is prescribed to patients with a higher pre-existing burden of suicide risk factors than patients prescribed SSRIs. As such these patients should be carefully evaluated for the presence or worsening of suicide-related behaviour (see sections 4.2 and 4.4).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antidepressants
ATC code: N06AX16
Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers. 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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.
Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors in vitro. Pharmacologic activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular effects.

5.2 Pharmacokinetic properties
Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

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.
Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 2 to 3 times that of a human dose of 225mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients
- Lactose, anhydrous
- Sodium starch glycolate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Magnesium stearate

Extragranular ingredients
- Cellulose, microcrystalline
- Sodium starch glycollate
- Yellow ferric oxide (E172)
- Red ferric oxide (E172)
- Purified talc
- Silica, colloidal anhydrous
- Magnesium stearate

6.2 Incompatibilities
- Not applicable

6.3 Shelf life
- 2 years

6.4 Special precautions for storage
- Store below 25°C. Store in the original package.

6.5 Nature and contents of container
- PVC/aluminium foil blisters (pack size 56 tablets)
- or
- PVC/ACLAR/aluminium foil blisters (pack size 56 tablets)

6.6 Special precautions for disposal
- Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
- Ranbaxy (UK) Limited.
- 20 Balderton Street,
- London W1K 6TL,
- United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
- PL 14894/0478

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
- 19/02/2008

10 DATE OF REVISION OF THE TEXT
- 19/02/2008
Module 3

PACKAGE INFORMATION LEAFLET

VENLAFAXINE
25/37.5/50/75 mg TABLETS

Read this entire 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 your pharmacist.

In this leaflet:
1. What Venlafaxine Tablets are and what are they used for
2. Before you take Venlafaxine Tablets
3. How to take Venlafaxine Tablets
4. Possible side effects
5. How to store Venlafaxine Tablets
6. Further Information

1. What Venlafaxine Tablets are and what are they used for

Venlafaxine hydrochloride is an antidepressant drug belonging to the class of medicines called Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs). Venlafaxine Tablets are used to treat the symptoms of depressive illness including depression accompanied by anxiety. Venlafaxine Tablets can relieve these symptoms and help you get better. Your doctor may continue to give you Venlafaxine Tablets when you are feeling better to prevent your symptoms from returning or prevent you from becoming depressed in the future.

2. Before you take Venlafaxine Tablets

Do not take Venlafaxine Tablets if any of the following apply to you

- You have previously had an allergic reaction to venlafaxine or any of the other ingredients in Venlafaxine Tablets. (An allergic reaction may include rash, itching, swelling of face, lips, or hands/feet, or breathing difficulties)
- You are taking or have recently taken (within the last two weeks) another antidepressant drug known as a monoamine oxidase inhibitor (MAOI). You should not take Venlafaxine Tablets at the same time as or within two weeks of stopping irreversible MAO inhibitors. Also do not take MAO inhibitors for at least one week after stopping Venlafaxine Tablets.
- You are under the age of 18 years.
- You have high blood pressure which is not properly controlled.
- You are taking medication to help you lose weight.
- You have a heart disease that predisposes you to development of serious abnormality in your heart rhythm. Such heart diseases include severe heart failure or recent heart attack.
- You suffer from rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption (which might cause pain in abdomen, cramps, diarrhea and gas after taking food).
- You have problems in passing urine due to obstruction of the urinary tract (e.g. due to enlarged prostate).
- You suffer from closed angle glaucoma (characterised by eye pain, dimness of vision, and haloes around lights).
If you think this applies to you, don’t take the tablets. Talk to your doctor and follow the advice given.

**Take special care with Venlafaxine Tablets if**
- You have **liver or kidney disease**. Your dose of Venlafaxine may be lowered.
- You have a history of **epilepsy** (seizure or fits). Your doctor will supervise you carefully while you are taking Venlafaxine.
- You are being treated with **electro convulsive therapy** (ECT).
- You suffer from or have a history of **mania**.
- You are pregnant or intend to become pregnant during treatment.
- You are **breastfeeding**.
- You suffer from high pressure in the eye (increased intraocular pressure) or have other risk factors (age above 40, family history, narrow drainage angles in their eyes etc.) for developing closed angle glaucoma.
- You have history of **bleeding disorders** e.g. bruising, stomach bleeds, recurrent nose bleeds or heavy periods or low platelet count.
- You have thoughts of **suicide or self-harm** at any time during the treatment period.
- You have felt **dizzy or unsteady on standing** due to a fall in blood pressure.
- You are **elderly**. Especially if you are taking water tablets (diuretics) or have recently suffered from severe vomiting or diarrhoea.
- You have problems with your **heart rhythm**.
- You have a history of **drug abuse**.
- You have a history of **aggressive behaviour**.

In studies, an increase in blood cholesterol levels was observed in a number of patients receiving long-term treatment with venlafaxine (over 3 months or more). Your doctor may therefore decide to regularly monitor your cholesterol levels during longer-term treatment. Please consult your doctor, even if these statements were applicable to you anytime in the past.

**Taking other medicines**

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

Care is needed if:
- You are taking **cimetidine** (a stomach drug), and are elderly or have liver problems, as cimetidine might increase the effect of Venlafaxine.
- You are, or have recently taken any medicines for the treatment of depression, particularly those known as **monoamine oxidase inhibitors (MAOIs)** or **selective serotonin reuptake inhibitors (SSRIs)**.
- You are taking **St John’s Wort** (*Hypericum perforatum*) used for the treatment of depression.
- You are taking medicines for **treatment of mental disorder like schizophrenia e.g. risperidone, haloperidol or clozapine**.
- You are taking medicines for **mood disorders e.g. lithium**.
- You are taking medicines known as **triptans for treatment of migraine e.g. sumatriptan**.
- You are taking blood thinning agents like anti-coagulants (e.g. warfarin, heparin etc.) or antiplatelet drugs (e.g. aspirin, ticlopidine etc.).
- You are taking any other medicines: certain medicines can affect the way venlafaxine passes through your body e.g. **ketocnazole** (for treatment of fungal infection), **erythromycin** (antibiotic).
- You are taking **indinavir** which is used for treatment of Human Immunodeficiency Virus (HIV) infection.

**Pregnancy and Breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant, intend to become pregnant or are currently breast-feeding. If you are already taking Venlafaxine Tablets and have just found out you are pregnant, you should talk to your doctor immediately.

**Driving and using machines**

Possible side effects of Venlafaxine Tablets include confusion, dizziness and blurred vision. If you get these side effects do not drive or use machinery.

**Venlafaxine Tablets and alcohol**

You should avoid alcohol while you are taking Venlafaxine Tablets.

**Important information about some of the ingredients of Venlafaxine Tablets**

Your medicine contains small quantities of an inactive ingredient known as **lactose**. If your doctor has told you that you have **intolerance to some sugars**, contact your doctor before taking this medicinal product.
3. How to take Venlafaxine Tablets

Dosage
Always take Venlafaxine Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual starting dose is one 37.5 mg tablet twice a day. You should take one tablet in the morning and one in the evening. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. The maximum daily dose should not exceed 375 mg. If you have the impression that the effect of Venlafaxine Tablet is too strong or too weak, talk to your doctor or pharmacist.

Your doctor may wish to monitor your blood pressure and heart rate particularly if you require treatment with high (greater than 200 mg a day) doses of Venlafaxine.

Patient with kidney or liver problems:
If you have kidney or liver problems your dose would be lower than that for other adults. Please follow your doctor's instructions.

Method and/or route(s) of administration
For oral use only. The tablets should be taken with food. Swallow the tablet whole with a glass of water.
Do not crush or chew them.

Duration of treatment:
You may need to take Venlafaxine for several months. If so, don't worry. This is not uncommon. It may take a few weeks or more before you feel your medicine is having an effect.

Until the full effect of your medicine becomes apparent, it is possible that the symptoms of your illness which may include thoughts of harming yourself or committing suicide will increase in the first few weeks of treatment. Tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time. During this time your doctor should monitor your progress. Treatment with Venlafaxine may be discontinued if your condition does not improve.

Use in children and adolescents under 18 years of age
Venlafaxine Tablets 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 Venlafaxine Tablets for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Venlafaxine Tablets 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 Venlafaxine Tablets. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Venlafaxine Tablets in this age group have not yet been demonstrated.

If you have taken more Venlafaxine Tablets than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

If you forget to take Venlafaxine Tablets at the correct time, do not worry and take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Venlafaxine Tablets
Do not stop taking your tablets without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Venlafaxine he will ask you to reduce your dose before stopping treatment altogether.

If Venlafaxine is stopped suddenly or the dose reduced too quickly, some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, dry mouth, loss of appetite, feeling or being sick, diarrhoea, nervousness, confusion, tinnitus (ringing in the ears), tingling, weakness, poor co-ordination, tremor, sweating or seizures. These symptoms are generally non-serious and disappear within a few days.

Your doctor will advise you on how you should gradually discontinue Venlafaxine treatment and if you experience any of these or other symptoms, which are troublesome, return to 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, Venlafaxine Tablets can cause side effects, although not everybody gets them. If any of the following happen, stop taking Venlafaxine Tablets and tell your doctor immediately, or go to the casualty department at your nearest hospital:

- **Allergic reaction** may manifest as skin rash, swollen face or tongue, or shortness of breath or difficulty breathing.
- Occasionally, **thoughts of suicide and self-harm** may occur or increase in the first few weeks of treatment for depression, until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences.
- If you have **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 a serious condition known as neuroleptic malignant syndrome.
- **Mania or hypomania** (feeling ‘high’ or very over excited).
- An abrupt onset of severe eye pain and headache, redness, blurred vision, rainbow-coloured halos around lights, and sudden loss of vision. These may be manifestations of an eye condition called closed angle glaucoma.

You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- unusual bruising or bleeding
- black, tarry stools, which is a symptom of gastrointestinal bleeding
- severe abdominal pain with nausea and/or vomiting, fever, which may be symptoms of inflammation of the pancreas
- increase in blood pressure
- rapid or irregular heart beat, flushing or fainting
- change in appetite or bowel habits, constipation, diarrhoea, indigestion, feeling or being sick, weight loss or gain
- unusual tiredness or weakness, headache, abdominal discomfort, clenching or grinding of teeth, yawning, chills, fever
- itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis)
- sore muscles or joints, muscle spasm
- dark or red coloured urine, muscle tenderness, weakness or stiffness which are symptoms of rhabdomyolysis
- stiff muscles, rarely dizziness or loss of balance, slurring or difficulty speaking, tremor, strange feeling on the skin such as "pins and needles" or burning
- dizziness, dry mouth, difficulty sleeping or abnormal dreams, drowsiness, nervousness, agitation, confusion, hallucinations
- seizures
- euphoric feelings, drowsiness, sustained rapid eye movement, dizziness, restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotonin syndrome
- disorientation and confusion often accompanied by hallucinations (delirium)
- difficulty in urinating, or feeling the need to go to the toilet more often than usual
- abnormal ejaculation, orgasm, reduced sex drive, impotence, menstrual disturbances in women, rarely abnormal breast milk production
- difficulty in breathing (dyspnoea)
- sweating, skin rash, itching, increased sensitivity of your skin to sunlight
- blurred vision, tinnitus (ringing in the ears)
- altered taste sensation
- abnormal hair loss
- severe skin rash which may lead to blistering and peeling of the skin.

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

Tell your doctor or pharmacist you are taking Venlafaxine before taking any other drug, if you become pregnant, or if you enter hospital for treatment.

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 Venlafaxine Tablets

Keep out of the sight and reach of children.
Do not take after the expiry date that is printed on the packaging.
Store below 25°C. Store in the original package.
If your doctor tells you to stop taking the tablets, please take them back to the pharmacist.

6. Further information

What Venlafaxine Tablets contain:
The active substance is Venlafaxine hydrochloride.
The other ingredients are:
- Intragranular ingredients: Lactose, anhydrous, Sodium starch glycolate, Yellow ferric oxide (E172), Red ferric oxide (E172), Magnesium stearate;
- Extragranular ingredients: Cellulose, microcrystalline, Sodium starch glycolate, Yellow ferric oxide (E172), Red ferric oxide (E172), Purified talc, Silica, colloidal anhydrous, Magnesium stearate.

What Venlafaxine Tablets look like and contents of the pack
Venlafaxine Tablets are peach coloured, uncoated, shield shaped tablets available in four strengths: 25mg, 37.5mg, 50mg and 75mg.
Venlafaxine 25mg Tablets are debossed with 'V' and '1' on one side and plain on other side. Each 25mg tablet contains venlafaxine hydrochloride equivalent to 25mg venlafaxine.
Venlafaxine 37.5mg Tablets are debossed with 'Y' and '2' on one side and plain on other side. Each 37.5mg tablet contains venlafaxine hydrochloride equivalent to 37.5mg venlafaxine.
Venlafaxine 50mg Tablets are debossed with 'V' and '3' on either side of breakline and breakline on other side. Each 50mg tablet contains venlafaxine hydrochloride equivalent to 50mg venlafaxine.
Venlafaxine 75mg Tablets are debossed with 'V' and '4' on either side of breakline and breakline on other side. Each 75mg tablet contains venlafaxine hydrochloride equivalent to 75mg venlafaxine.
Venlafaxine Tablets are available in pack sizes of 14, 28, 30, 42, 56, 60 and 100. Not all pack sizes may be supplied.

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

This medicinal product is authorised in the Member States of the EEA under the following names:
- Austria: Venlafaxin® "Ranbaxy" 25/37.5/50/75mg Tablets
- Ireland: Venlafaxine 37.5/75mg Tablets
- Italy: Venlafaxina Ranbaxy 37.5/75mg compresse

This leaflet was last approved in 15/02/2008
Package Information Leaflet

RANBAXY

Ranoven
37.5/75 mg tablets

Venlafaxine

Read this entire 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 your pharmacist.

In this leaflet:
1. What Ranoven Tablets are and what are they used for
2. Before you take Ranoven Tablets
3. How to take Ranoven Tablets
4. Possible side effects
5. How to store Ranoven Tablets
6. Further Information

1. What Ranoven Tablets are and what are they used for

Venlafaxine hydrochloride is an antidepressant drug belonging to the class of medicines called Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs).

Ranoven Tablets are used to treat the symptoms of depressive illness including depression accompanied by anxiety. Ranoven Tablets can relieve these symptoms and help you get better. Your doctor may continue to give you Ranoven Tablets to prevent your symptoms from returning or in the future.

2. Before you take Ranoven Tablets

Do not take Ranoven Tablets if any of the following apply to you:
- You have previously had an allergic reaction to venlafaxine or any of the other ingredients in Ranoven Tablets. (An allergic reaction may include rash, itching, swelling of face, lips, or hands/feet, or breathing difficulties)
- You are taking or have recently taken (within the last two weeks) another antidepressant drug known as a monoamine oxidase inhibitor (MAOI). You should not take Ranoven Tablets at the same time as or within two weeks of stopping irreversible MAO inhibitors. Also do not take MAO inhibitors for at least one week after stopping Ranoven Tablets.
- You are under the age of 18 years.
- You have high blood pressure which is not properly controlled.
- You are taking medication to help you lose weight.
- You have a heart disease that predisposes you to development of serious abnormality in your heart rhythm. Such heart diseases include severe heart failure or recent heart attack.
- You suffer from rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption (which might cause pain in abdomen, cramps, diarrhea and gas after taking food).
- You have problems in passing urine due to obstruction of the urinary tract (e.g. due to enlarged prostate).
- You suffer from closed angle glaucoma (characterised by eye pain, dimness of vision, and haloes around lights).

If you think this applies to you, don’t take the tablets, talk to your doctor and follow his advice. If he is still of the opinion that you cannot take Ranoven Tablets, you should obtain your medication from another source.

Take special care with Ranoven Tablets if:
- You have liver or kidney disease. Your dose of Venlafaxine may be lowered.
- You have a history of epilepsy (seizure or fits). Your doctor will supervise you carefully while you are taking Ranoven Tablets.
- You are being treated with electroconvulsive therapy (ECT).
- You suffer from a history of mania.
- You suffer from high pressure in the eye (increased intraocular pressure) or have other risk factors (age above 40, family history, narrow drainage angles in their eyes etc.) for developing closed angle glaucoma.
- You are pregnant or intend to become pregnant during treatment.
- You are breastfeeding.
- You have history of bleeding disorders e.g. bruising, stomach bleed, recurrent nose bleed or heavy period or favourable to toxic.
- You have history of suicide or self-harm at any time during the treatment period.
- You have fell dizzy or faintly while standing due to fall in blood pressure.
- You are elderly. Especially if you are taking water tablets (diuretics) or have recently suffered from severe vomiting or diarrhoea.
- You have problems with your heart rhythm.
- You have a history of drug abuse.
- You have a history of aggressive behaviour.

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Insudies, an increase in blood cholesterol levels was observed in a number of patients receiving long-term treatment with venlafaxine (over 3 months or more). Your doctor may therefore decide to regularly monitor your cholesterol levels during longer-term treatment. Please consult your doctor, even if these statements were applicable to you at any time in the past.

**Taking other medicines**

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

**Caution needed:**
- You are taking **clomipramine** (a stomach drug), **and are elderly or have liver problems**, as clomipramine may increase the effect of venlafaxine.
- You are, or have recently taken any medications for the treatment of depression, particularly those known as monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs).
- You are taking St John’s Wort (*Hypericum perforatum*) used for the treatment of depression.
- You are taking medicines for treatment of mental disorder like schizophrenia e.g. risperidone, haloperidol or clozapine.
- You are taking medicines for mood disorders e.g. lithium.
- You are taking medicines known as triptans for the treatment of migraine e.g. sumatriptan.
- You are taking blood thinning agents like anticoagulants (e.g. warfarin, heparin etc.) or antiplatelet drugs (e.g. aspirin, ticlopidine etc.)
- You are taking any other medicines: certain medicines can affect the way venlafaxine passes through your body, e.g. ketoconazole (for treatment of fungal infection), erythromycin (antibiotic).
- You are taking indinavir which is used for treatment of Human Immunodeficiency Virus (HIV) infection.

**Pregnancy and Breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant, intend to become pregnant or are currently breast-feeding. If you are already taking Ranovan Tablets and have just found out you are pregnant, you should talk to your doctor immediately.

**Driving and using machines**

Possible side effects of Ranovan Tablets include confusion, dizziness and blurred vision. If you get these side effects do not drive or use machinery.

**Ranovan Tablets and alcohol**

You should avoid alcohol while you are taking Ranovan Tablets.

**Important information about some of the ingredients of Ranovan Tablets**

Your medicine contains small quantities of an inactive ingredient known as lactose. If you have told your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

### 3. How to take Ranovan Tablets

**Dosage**

Always take Ranovan Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

The usual starting dose is one 37.5 mg tablet twice a day. You should take one tablet in the morning and one in the evening. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. The maximum daily dose should not exceed 375 mg. If you have the impression that the effect of Ranovan Tablets is too strong or too weak, talk to your doctor or pharmacist.

Your doctor may wish to monitor your blood pressure and heart rate particularly if you require treatment with high (greater than 200 mg a day) doses of venlafaxine.

**Patient with kidney or liver problems:**

If you have kidney or liver problems, your dose would be lower than that for other adults. Please follow your doctor’s instructions.

**Method and route(s) of administration**

For oral use only. The tablets should be taken with food. Swallow the tablet whole with a glass of water. Do not crush or chew them.

**Duration of treatment:**

You may need to take Venlafaxine for several months. Also, don’t worry, this is not uncommon. It may take a few weeks or more before you feel your medicine is having an effect.

Until the full effect of your medicine becomes apparent, it is possible that the symptoms of your illness which may include thoughts of harming yourself or committing suicide will increase in the first few weeks of treatment. Tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time. During this time your doctor should monitor your progress. Treatment with Venlafaxine may be discontinued if your condition does not improve.

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

Ranovan Tablets 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 Ranovan Tablets for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Ranovan Tablets 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 Ranovan Tablets. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of
Ranoven Tablets in this age group have not yet been demonstrated.

**If you have taken more Ranoven Tablets than you should**, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

**If you forget to take Ranoven Tablets at the correct time**, do not worry and take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

**If you stop taking Ranoven Tablets**
Do not stop taking your tablets without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Venlafaxine he will ask you to reduce your dose before stopping treatment altogether.

Venlafaxine is stopped suddenly or the dose reduced too quickly, some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, dry mouth, loss of appetite, feeling or being sick, diarrhoea, nervousness, confusion, tinnitus (ringing in the ears), tingling, weakness, poor co-ordination, tremor, sweating or seizures. These symptoms are generally non-serious and disappear within a few days.

Your doctor will advise you on how you should gradually discontinue Venlafaxine treatment and if you experience any of these or other symptoms, which are troublesome, return to 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, Ranoven Tablets can cause side effects, although not everybody gets them.

If any of the following happen, stop taking Ranoven Tablets and tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Allergic reaction may manifest as skin rash, swollen face or tongue, or shortness of breath or difficulty breathing.
- Occasionally, thoughts of suicide and self-harm may occur or increase in the first few weeks of treatment for depression, until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences.
- If you have 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 a serious condition known as neuroleptic malignant syndrome.
- Mania or hypomania (feeling ‘high’ or very over excited).
- An abrupt onset of severe eye pain and headache, redness, blurred vision, rainbow-colored halos around lights, and sudden loss of vision. These may be manifestations of an eye condition called closed angle glaucoma.

You may need urgent medical attention or hospitalization.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- unusual bruising or bleeding
- black, tarry stools, which is a symptom of gastrointestinal bleeding
- severe abdominal pain with nausea and/or vomiting, fever, which may be symptoms of inflammation of the pancreas
- increase in blood pressure
- rapid or irregular heart beat, flushing or fainting
- change in appetite or bowel habits, constipation, diarrhoea, indigestion, feeling or being sick, weight loss or gain
- unusual tiredness or weakness, headache, abdominal discomfort, clenching or grinding of teeth, yawning, chill, fever
- itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis)
- sore muscles or joints, muscle spasm
- dark or red coloured urine, muscle tenderness, weakness or stiffness which are symptoms of rhabdomyolysis
- stiff muscles, rarely clumsiness or loss of balance, slurring or difficulty speaking, tremor, strange feeling on the skin such as "pins and needles" or burning
- dizziness, dry mouth, difficulty sleeping or abnormal dreams, drowsiness, nervousness, agitation, confusion, hallucinations
- seizures
• euphoric feelings, drowsiness. sustained rapid eye movement, clumsiness restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotonin syndrome
• disorientation confusion often accompanied by hallucination (delirium)
• difficulty in urinating or feeling the need to go to the toilet more often than usual
• abnormal ejaculation orgasm, reduced sex drive, impotence, menstrual disturbances in women, rarely abnormal breast milk production
• difficulty in breathing (dyspnoea)
• sweating, skin rash, itching, increased sensitivity of your skin to sunlight
• blurred vision, tinnitus (ringing in the ears)
• altered taste sensation
• abnormal hair loss
• severe skin rash which may lead to blistering and peeling of the skin.

Venlafaxine sometimes causes unwanted effects which you may not be aware of, such as increases in blood pressure or abnormal heart beat. slight changes in blood levels of liver enzymes, sodium or rarely cholesterol. More rarely, Venlafaxine may reduce the number of platelets in your blood. Therefore, your doctor may wish to do blood tests occasionally, particularly if you have been taking Venlafaxine for a long time.

Tell your doctor or pharmacist you are taking Venlafaxine before taking any other drug, if you become pregnant, or you enter hospital for treatment.

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 Ranoven Tablets

Keep out of the sight and reach of children.
Do not take after the expiry date that is printed on the packaging.
Store below 25°C. Store in the original package.
If your doctor tells you to stop taking the tablets, please take them back to the pharmacist.

6. Further Information

What Ranoven Tablets contain:
The active substance is Venlafaxine hydrochloride.
The other ingredients are: Lactose, anhydrous, Sodium starch glycolate, Yellow ferric oxide (E172), Red ferric oxide (E172), Magnesium stearate; Extragranular ingredients: Cellulose, microcrystalline, Sodium starch glycolate, Yellow ferric oxide (E172), Red ferric oxide (E172), Purified talc, Silica, colloidal anhydrous, Magnesium stearate.

What Ranoven Tablets look like and contents of the pack:
Ranoven Tablets are peach coloured, uncoated, shield shaped tablets available in two strengths: 37.5mg and 75mg.
Ranoven 37.5mg Tablets are debossed with 'V' and '2' on one side and plain on other side. Each 37.5mg tablet contains venlafaxine hydrochloride equivalent to 37.5mg venlafaxine.
Ranoven 75mg Tablets are debossed with 'V' and '4' on either side of breakline, & breakline on other side. Each 75mg tablet contains venlafaxine hydrochloride equivalent to 75mg venlafaxine.
Ranoven Tablets are available in pack size of 56 tablets only.

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

This medicinal product is authorised in the Member States of the EEA under the following names:
Ireland: Venlafaxine 37.5/75mg Tablets

This leaflet was last approved in 19/02/2008
Module 4

LABELLING

PL 14894/0473-6
Venlafaxine 37.5 mg Tablets
Each tablet contains, as the active ingredient:
Venlafaxine hydrochloride equivalent to Venlafaxine 37.5 mg.
The tablets also contain lactose anhydrous. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

RANBAXY
Venlafaxine
37.5 mg Tablets

For oral use only
DO NOT EXCEED THE STATED DOSE.
Use as directed by a physician.
Store below 25°C. Store in original package.

Braille translation is
venlafaxine
≤37.5 mg
tablets
* denotes unique numer sign
Venlafaxine 25, 37.5, 50 and 75mg Tablet

Press tablet through foil from the other side

Press tablet through foil from the other side

Press tablet through foil from the other side

Venlafaxin 50 mg Tablets
Blister Size: 121 x 49 mm
Foil Width: 127 mm
Market: UK
RLL/PKGDEV - 29/09/07
A04/10/07

BATCH no. and Exp
will be printed at the time of blister sealing.
Venlafaxine 75 mg Tablets

Carton Size: 125 x 45 x 63 mm
Market: UK
RLL/PKGDEV - J29/05/2007
A13/16/2007 (Valid Date)

Braille translation is
ventlafaxine
≠75 mg
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**Venlafaxin 75 mg Tablets**
- Blister Size: 121 x 49 mm
- Foil Width: 127 mm
- Market: UK
- RLL/PKGDEV - 29/09/07
- A04/10/07

**BATCH no. and Exp will be printed at the time of blister sealing.**
Each tablet contains, as the active ingredient, venlafaxine hydrochloride equivalent to venlafaxine 37.5 mg.

The tablets also contain excipients. If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking this medicinal product.

DO NOT EXCEED THE STATED DOSE.

Use as directed by a physician.

Store below 25°C. Store in original package.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Please read the enclosed leaflet before taking the medicine.
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Press tablet through foil from the other side

**Ranoven 37.5 mg Tablets**  
**Blister Size:** 121 x 49 mm  
**Foil Width:** 127 mm  
**Market:** UK  
**RLL/PKGDEV - J29/09/07**  
**A04/10/07**

**BATCH no. and Exp will be printed at the time of blister sealing.**
Ranoven 75 mg Tablets
Blister Size: 121 x 49 mm
Foil Width: 127 mm
Market: UK
RLL/PKGDEV - J29/09/07
A04/10/07

BATCH no. and Exp will be printed at the time of blister sealing.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Venlafaxine/Ranoven Tablets, in the treatment of major depressive disorder including depression accompanied by anxiety, is approvable.

These are applications made under Article 10.1 of 2001/83 EC, as amended, for Venlafaxine/Ranoven Tablets. The originator product is Effexor Tablets, marketed by Wyeth Pharmaceuticals, France. The tablets were licensed in 1994 and have thus been authorised in the EU for more than 10 years. A bioequivalence study was performed using Effexor 50 mg tablets (France) as the reference. The relevant products in the UK are Effexor 25, 37.5, 50 & 75 mg Tablets (PL 00011/0198-0201). The UK acts as RMS. The 37.5 mg and 75 mg strength applications are submitted in duplicate in the RMS and Republic of Ireland; these applications are identical. No genetically modified organisms are included in these products. No paediatric development plan exists for these products.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application is a generic medicinal product of reference product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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 manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Venlafaxine 25 / 37.5 / 50 / 75 mg Tablets
Ranoven 37.5 / 75 mg Tablets |
| Name(s) of the active substance(s) (INN)          | Venlafaxine hydrochloride |
| Pharmacotherapeutic classification (ATC code)    | N06AX16 |
| Pharmaceutical form and strength(s)              | 25 / 37.5 / 50 / 75 mg Tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/0974/01-04/DC and UK/H/975/01-02/DC |
| Reference Member State                           | United Kingdom |
| Member States Concerned                          | UK/H/974/01 & 03: Austria
UK/H/974/02 & 04: Austria, Italy, Republic of Ireland
UK/H/975/01 & 02: Republic of Ireland |
| Marketing Authorisation Number(s)                | PL 14894/0473-6 and PL 14894/0477-8 |
| Name and address of the authorisation holder     | Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom |
III   SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

Nomenclature and Structure

\[
\text{rINN: Venlafaxine hydrochloride}
\]

Chemical names
1-[(1RS)-2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride

CAS No.: 99300-78-4

\[\text{C}_{17}\text{H}_{27}\text{NO}_2\cdot\text{HCl}\]

Molecular Weight: 313.9

General Properties

Venlafaxine hydrochloride is a white or almost white powder. It is sparingly soluble in water and in methanol, soluble in anhydrous ethanol, and slightly soluble or practically insoluble in acetone. Ranbaxy’s venlafaxine hydrochloride is said to be a racemic mixture and conforms to the Ph. Eur. monograph. Venlafaxine hydrochloride is known to exhibit polymorphism. Ranbaxy Laboratories Limited states that Form C is produced.

This is subject to DMF. A letter of access has been provided

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Venlafaxine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Stability studies have been performed with the drug substance the proposed retest period of 24 months is justified.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, colloidal anhydrous silica, ferric oxide pigment red E172, microcrystalline cellulose, yellow ferric oxide E172, talc purified, magnesium stearate, and sodium starch glycolate. All excipients used comply with their respective European Pharmacopoeia monograph or USNF monograph. Satisfactory certificates of analysis have been provided for all excipients.

Lactose anhydrous and magnesium stearate are the only materials of animal or human origin contained in or used in the manufacturing process for the proposed products. Suitable declarations have been provided from the appropriate suppliers of all the excipients.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce Venlafaxine/Ranoven Tablets that could be considered as generic products to the originator product Effexor Tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

**Dissolution and impurity profiles**

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Product is packaged in to PVC/Aclar/Aluminium blisters and PVC aluminium foil blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage condition of store in the original package and store below 25 degree C have been set. This is acceptable.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patients groups (“user testing”), in accordance with article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows the patients/users are able to act upon the information that it contains.

Conclusion
The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisations should be granted for these applications.
PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic products. The non-clinical overview provides a reasonable review of the known pharmacological and toxicological properties of Venlafaxine.
CLINICAL ASPECTS

1. INTRODUCTION
These are applications for Venlafaxine 25 mg, 37.5 mg, 50 mg & 75 mg Tablets (PL 14894/0473-6) and Ranoven 37.5 mg and 75 mg Tablets (PL 14894/0477-8) using the decentralised procedure. These were submitted on the basis of Directive 2001/83/EC Article 10(1) generic application. The applicant considers these products as generic medicinal products of the originator product Effexor by Wyeth Pharmaceuticals, France, registered since 05/05/94.

2. BACKGROUND
Venlafaxine is a phenylethylamine derivative which facilitates neurotransmission in the brain by blocking presynaptic reuptake of serotonin and noradrenaline. Its potency in inhibiting serotonin reuptake is approximately 5 times that of its noradrenaline reuptake inhibitory activity.

3. INDICATIONS
The applicant has submitted the following:

Venlafaxine/Ranoven Tablets are indicated for the treatment of major depressive disorder including depression accompanied by anxiety.
Following an initial response Venlafaxine/Ranoven Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

4. DOSE & DOSE SCHEDULE
See the SPC for full details. The recommended dosages and dose schedules are consistent with those for Effexor Tablets.

5. CLINICAL PHARMACOLOGY
Pharmacodynamics
The pharmacodynamics of Venlafaxine/Ranoven are well established in various situations and specifically in the indications sought.

Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

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, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

The applicant has provided a single bioequivalence study in support of these applications. A single bioequivalent study comparing 50mg strengths of Venlafaxine tablets with the reference product Effexor 50mg Tablets. Acceptance criteria are satisfactory and the results support the claim for bioequivalence between test and reference products.

The results of study CPU-M-049/VENL-50/05 with the 50mg formulation can be extrapolated to other strengths 25, 37.5, and 75mg according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

7. **SAFETY**

No new data are submitted and none are required for these types of applications. The safety of Venlafaxine has been well established for use in the indications sought and sufficient published literature has been submitted in support of this. The bioequivalence studies did not raise any new safety concerns.

**BENEFIT RISK ASSESSMENT**

The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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