UKPAR Venlafaxine 25mg, 37.5mg, 50mg & 75mg Tablets

VENLAFAXINE 25MG TABLETS
PL 00289/0711
PL 00289/0715

VENLAFAXINE 37.5MG TABLETS
PL 00289/0712
PL 00289/0716

VENLAFAXINE 50MG TABLETS
PL 00289/0713
PL 00289/0717

VENLAFAXINE 75MG TABLETS
PL 00289/0714
PL 00289/0718

UKPAR

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PL 00289/0713
PL 00289/0717

VENLAFAXINE 75MG TABLETS
PL 00289/0714
PL 00289/0718

LAY SUMMARY

The MHRA granted Teva UK Ltd Marketing Authorisations (licences) for the medicinal products Venlafaxine 25mg Tablets (PL 00289/0711 and PL 00289/0715), Venlafaxine 37.5mg Tablets (PL 00289/0712 and PL 00289/0716), Venlafaxine 50mg Tablets (PL 00289/0713 and PL 00289/0717) and Venlafaxine 75mg Tablets (PL 00289/0714 and PL 00289/0718). These are prescription only medicines (POM) for the treatment of symptoms of depressive illness, including depression accompanied by anxiety.

Venlafaxine 25mg, 37.5mg, 50mg and 75mg Tablets contain the active ingredient venlafaxine which is an antidepressant.

The test products were considered to be the same as the original products Efexor 25mg, 37.5mg, 50mg and 75mg Tablets (John Wyeth & Brother Ltd) based on the bioequivalence study submitted taking into account that linear kinetics apply over the dose range.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Venlafaxine 25mg, 37.5mg, 50mg and 100mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
VENLAFAXINE 25MG TABLETS
PL 00289/0711
PL 00289/0715

VENLAFAXINE 37.5MG TABLETS
PL 00289/0712
PL 00289/0716

VENLAFAXINE 50MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Venlafaxine 25mg Tablets (PL 00289/0711 and PL 00289/0715), Venlafaxine 37.5mg Tablets (PL 00289/0712 and PL 00289/0716), Venlafaxine 50mg Tablets (PL 00289/0713 and PL 00289/0717) and Venlafaxine 75mg Tablets (PL 00289/0714 and PL 00289/0718) to Teva UK Ltd on 30 October 2007. The products are prescription only medicines.

Applications for four strengths of venlafaxine, and one set of duplicates, were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic products of Efexor 25mg, 37.5mg, 50mg and 75mg Tablets (Wyeth Pharmaceuticals BV) authorised in the Netherlands in June 1994. The UK reference products, Efexor 25mg, 37.5mg, 50mg and 75mg Tablets (John Wyeth & Brother Ltd), have been authorised since November 1994 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient venlafaxine and are indicated for the treatment of depressive illness, including depression accompanied by anxiety. They are also indicated for use following and initial response in prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI). It is used to treat depressive illness via potentiation of its neurotransmitter activity in the central nervous system. Both venlafaxine and its main metabolite have equal efficacy.

The applications were submitted at the same time and all depend on the bioequivalence study that compares the applicant’s products with the reference product Efexor 37.5mg (John Wyeth & Brother Ltd). Consequently, all sections of the Scientific Discussion refer to all applications.
**PHARMACEUTICAL ASSESSMENT**

**COMPOSITION**

The products are formulated as immediate-release tablets containing 25mg, 37.5mg, 50mg and 75mg of the active pharmaceutical ingredient venlafaxine (presented as the hydrochloride salt). The excipients present are lactose monohydrate, colloidal anhydrous silica, magnesium stearate, sodium starch glycolate type A, Yellow Iron Oxide and Red Iron Oxide.

The tablets are presented in aluminium-foil sealed PVC/PVdC blisters. Venlafaxine 25mg Tablets are available in packs of 30 and 60 tablets. Venlafaxine 37.5mg Tablets are available in packs of 10, 20, 28, 30, 50, 56, 60 and 100 tablets. Venlafaxine 50mg Tablets are available in packs of 28, 30, 42, 56, 60 and 100 tablets. Venlafaxine 75mg Tablets are available in packs of 20, 28, 30, 50, 56, 60 and 100 tablets. Additionally, all strengths are available in a Hospital pack of 50 tablets and Venlafaxine 75mg Tablets are available in a Hospital pack of 500 tablets.

**DRUG SUBSTANCE**

**Venlafaxine**

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 Pharmacopeia specification is provided for venlafaxine.

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

Batch analysis data are provided for three batches and comply with the proposed specification.

Venlafaxine is stored in polyethylene bags inside aluminium laminated bags.

Stability data have been generated supporting a retest period of 3 years when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards with the exception of the colorants (Yellow iron oxide and Red iron oxide) which are tested as per acceptable in-house specifications.
Satisfactory certificates of analysis have been provided for all excipients.

Lactose monohydrate and magnesium stearate contain material of animal or human origin. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for magnesium stearate confirming that the risk of transmitting TSEs is sufficiently low.

**Dissolution profiles**
Dissolution profiles for the drug product were found to be similar to the reference product.

**Manufacture**
A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory process validation has been carried out.

**Finished product specification**
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data from two batches of each strength have demonstrated compliance with the proposed release specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

**Container Closure System**
Satisfactory specifications and Certificates of Analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability data support the proposed shelf-life of 3 years with no special storage conditions.

**Bioequivalence/bioavailability**
Refer to the clinical assessment report.

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

**CONCLUSION**
The proposed products have been shown to be generic products of the reference products and have met the requirements with respect to qualitative and quantitative content of the active substance.
It is recommended that Marketing Authorisations should be granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are abridged applications for immediate-release tablets containing 25mg, 37.5mg, 50mg, and 75mg of the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine submitted under the provisions of Directive 2001/83/EC Article 10.1, claiming to be generic products of the UK brand leader Efexor 25mg, 37.5mg, 50mg and 75mg Tablets.

Venlafaxine is well characterised in the literature. It is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic or other available antidepressants. It is a racemate with two active enantiomers.

INDICATIONS

The applicant has submitted the following:

Venlafaxine is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response venlafaxine is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

These indications are consistent with those for the innovator product.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications is consistent with the innovator product.

CLINICAL PHARMACOLOGY

Pharmacodynamics

No new data were submitted. The pharmacodynamics of venlafaxine are well described. The mechanism of its antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite O-desmethylvenlafaxine (ODV) are potent neuronal SNRIs and weak inhibitors of dopamine re-uptake. In addition, venlafaxine and ODV 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. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular side effects.
Pharmacokinetics
No new data were submitted. The pharmacokinetics of venlafaxine are well described. It is well absorbed (>92%) and undergoes extensive first-pass metabolism. Bioavailability is unaffected by food. Considerable intrasubject variability is seen. 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. ODV is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and ODV is approximately 5 and 11 hours, respectively. Mean peak ODV plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Venlafaxine and ODV are 27% and 30% bound to plasma proteins respectively. ODV, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

Bioequivalence
A single bioequivalence study is presented for the 37.5mg strength, carried out in compliance with Good Clinical Practice (GCP).

As the present applications for all strengths are supported by a single biostudy on the 37.5mg strength, it is necessary to consider the linearity of kinetics over the therapeutic range (i.e. up to the maximum recommended dose of 375mg per day). Venlafaxine is virtually completely absorbed at therapeutic doses from either tablet or oral solution. It has been established that the kinetics of venlafaxine and the active metabolite are linear up to 450mg and therefore a further study is not required for the other strengths if the excipients are qualitatively and quantitatively the same in both and dissolution behaviour is similar.

As the Efexor SPC advises that “it is recommended that Efexor be taken with food” the biostudy was done under standard fed conditions. This is appropriate since the bioavailability of venlafaxine is unaffected by food.

Study
In this comparative, two-way, two-period, single dose crossover study, 24 healthy fed male volunteers were randomised to receive 37.5mg orally of either the applicant's test product, Venlafaxine 37.5mg Tablets, or the reference product Efexor 37.5mg Tablets (John Wyeth & Brother Ltd, UK). Serum drug levels were followed for 72 hours following dosing. This was sufficient to meet the 80% criterion for $\frac{AUC_t}{AUC_{inf}}$. The schedule was appropriate for accurate determination of $AUC_{inf}$ and $C_{max}$. The washout period between phases was sufficiently long at 1 week.

The randomisation scheme was balanced for sequence and appears random.

Data for $AUC_t$, $AUC_{inf}$ and $C_{max}$ were analysed by ANOVA, both log-transformed and non-transformed. $T_{max}$ was analysed non-parametrically.

Three subjects were withdrawn from the study due to adverse events (e.g. vomiting) following dosing in the first period and their samples were not analysed. Twenty-one subjects completed the study and their samples were analysed. This is satisfactory.
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals for both the parent compound and the active metabolite are presented in the following table:

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Test product (geometric means)</th>
<th>Reference product (geometric means)</th>
<th>Ratio Test/reference x 100</th>
<th>90% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venlafaxine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>566.50</td>
<td>578.48</td>
<td>97.93</td>
<td>94.09-101.93</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng.h/ml)</td>
<td>583.60</td>
<td>593.75</td>
<td>98.29</td>
<td>94.60-102.12</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>73.37</td>
<td>80.52</td>
<td>91.13</td>
<td>84.54-98.22</td>
</tr>
<tr>
<td>T$_{\text{max}}$ (h)*</td>
<td>2.46</td>
<td>2.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>O-desmethylvenlafaxine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>1426.221</td>
<td>1418.08</td>
<td>100.57</td>
<td>96.97-104.31</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng.h/ml)</td>
<td>1466.12</td>
<td>1454.23</td>
<td>100.82</td>
<td>97.27-104.49</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>71.62</td>
<td>72.74</td>
<td>98.46</td>
<td>95.65-101.35</td>
</tr>
<tr>
<td>T$_{\text{max}}$ (h)*</td>
<td>4.46</td>
<td>3.86</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The 90% Confidence Intervals for the log-transformed parameters C$_{\text{max}}$, AUC$_{0-t}$ and AUC$_{0-\infty}$ for venlafaxine and the metabolite ODV lie within the range 80.0-125.0%, such that the test and reference products may be considered bioequivalent after a single dose under fed conditions.

Given that the four strengths are based on a proportional formulation, similar dissolution profiles occur across the different strengths and linear kinetics apply over the proposed dose range, it is acceptable that a bioequivalence study has not been performed on the 25mg, 50mg or 75mg tablets.

Bioequivalence has been satisfactorily demonstrated in accordance with the Committee for Proprietary Medicinal Products (CPMP) criteria for both the parent compound and the active metabolite.

**CLINICAL EFFICACY**

No new efficacy data are presented for these applications and none are required.

**CLINICAL SAFETY**

No formal safety data are presented for these applications and none are required.

**CLINICAL EXPERT REPORT**

The clinical expert report has been written by an appropriately qualified pharmaceutical physician. It is an adequate review of the published data on venlafaxine and the bioequivalence study.
SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSION

The applicant has demonstrated that Venlafaxine 25mg, 37.5mg, 50mg and 75mg Tablets are bioequivalent to the reference products. Marketing Authorisations should be granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Venlafaxine 25mg, 37.5mg, 50mg and 75mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Venlafaxine 37.5mg Tablets and Efexor 37.5mg Tablets (John Wyeth & Brother Ltd). Since linear kinetics apply and the strengths are directly proportional to each other, bioequivalence studies for the 25mg, 50mg and 75mg tablets were not required.

No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the reference product are interchangeable. The risk benefit is, therefore, considered to be positive.
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PL 00289/0716

VENLAFAXINE 50MG TABLETS
PL 00289/0713
PL 00289/0717

VENLAFAXINE 75MG TABLETS
PL 00289/0714
PL 00289/0718

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 16 September 2004.

2 Following standard checks and communication with the applicant, the MHRA considered the applications valid on 21 October 2004.

3 Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 28 June 2005, 14 September 2006 and 23 April 2007, and further information relating to the clinical dossiers on 29 July 2005 and 23 April 2007.


5 The applications were determined on 30 October 2007.
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   PL 00289/0718

**STEPS TAKEN AFTER AUTHORISATION – SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
</table>

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains the equivalent of 25 mg of venlafaxine as 28.284 mg venlafaxine hydrochloride.

Excipients:
Each tablet contains 64.686 mg of lactose, monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Mottled peach, round, flat bevelled tablet, on one side scored and debossed “9” on one side of the score and “3” on the other side of the score. Debossed with “199” on the opposite side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Venlafaxine is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response venlafaxine is 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 should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75 mg per day given in two divided doses (37.5 mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine be taken with food.
If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150 mg per day given in two divided doses (75 mg 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 75 mg 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 375 mg per day. The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited number of tablets 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 sections 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:**

For patients with mild renal impairment (GFR>30 ml/minute) or mild hepatic impairment (PT<14 seconds), no change in dosage is necessary.

For patients with moderate renal impairment (GFR 10-30 ml/minute) or moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Insufficient data are available to support the use of venlafaxine in patients with severe renal impairment (GFR<10 ml/minute) or severe hepatic impairment (PT>18 seconds).

**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:**
Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.3 and 4.8).

The efficacy and safety of venlafaxine 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 for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine has been shown to be efficacious during long-term (up to 12 months) treatment.

In clinical trials venlafaxine was demonstrated 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 sections 4.4 and 4.8). Following treatment with daily doses of venlafaxine greater than 75 mg 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 section 4.5).
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. Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder (see section 4.8).

This medicinal product contains lactose monohydrate. 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.

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). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 31% of patients treated with venlafaxine and in approximately 17% of placebo patients. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia 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 sections 4.2 and 4.4).

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.
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.

7. Significant electrocardiogram findings were observed in 0.8% of venlafaxine-treated patients compared with 0.7% of placebo-treated patients. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

8. Dose-related increases in blood pressure have been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200 mg (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 in post-marketing experience.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 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 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. In clinical trials the mean heart rate was increased 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 intra-ocular 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 in placebo-controlled trials. 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of 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 in combination with an MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine before starting an MAOI (see also section 4.3).

**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/depramine:** 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_max were increased by approximately 35%.

**Haloperidol:** In a pharmacokinetic study co-administration of venlafaxine with a single 2 mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in C_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 temporally 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.

**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 metabolisers. 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 is 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 is administered with cimetidine.

Warfarin: Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin following the addition of venlafaxine.

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.

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 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 section 4.4.

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; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

**Cardiovascular and vascular disorders** (see section 4.4) - Common: hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, 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 section 4.4), weight gain or loss; Uncommon: hyponatraemia including SIADH (see section 4.4), increased liver enzymes (see below); Rare: hepatitis; Very rare: prolactin increased.


**Neurological disorders** - Very common: dizziness, dry mouth, insomnia, nervousness, 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, dystonia, mania or hypomania (see section 4.4), neuroleptic malignant syndrome-like effects, seizures (see section 4.4), serotonergic syndrome; Very rare: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4).
Renal and urinary disorders - **Common**: urinary frequency; **Uncommon**: urinary retention.

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

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

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

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

**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 sections 4.2 and 4.4).

**Special Notes:**

In all premarketing depression trials with venlafaxine tablets, seizures were reported in 0.3% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in venlafaxine treated patients in clinical trials for depression and GAD. No seizures occurred in placebo-treated patients in depression studies. Seizures were reported in 0.2% of placebo-treated patients in GAD studies (see section 4.4).
Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with venlafaxine is 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 and serotonin syndrome and changes in level of consciousness 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: Nervous system, Psychoanaleptics, Antidepressants, Other antidepressants
ATC code: M03B X02

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, 0-desmethylvenlafaxine, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and 0-desmethylvenlafaxine reduce β3-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 172 ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. 0-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. 0-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 225 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, monohydrate
Colloidal silica, anhydrous
Magnesium stearate
Sodium starch glycolate (Type A)
Yellow iron oxide (E172)
Red iron oxide (E172)
6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions.

6.5 Nature and contents of container
Transparent PVC/PVdC-aluminium blisters.
Blister packs of 30 & 60 tablets. Hospital packs of 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0711
PL 00289/0715

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/10/2007

10 DATE OF REVISION OF THE TEXT
30/10/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 37.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains the equivalent of 37.5 mg of venlafaxine as 42.426 mg venlafaxine hydrochloride.

Excipients:
Each tablet contains 97.029 mg of lactose, monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Mottled peach, round, flat bevelled tablet, on one side scored and debossed “9” on one side of the score and “3” on the other side of the score. Debossed with “7380” on the opposite side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Venlafaxine is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response venlafaxine is 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 should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75 mg per day given in two divided doses (37.5 mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine be taken with food.

If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150 mg per day given in two divided doses (75 mg 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 75 mg 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 375 mg per day. The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited number of tablets 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 sections 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:**

For patients with mild renal impairment (GFR >30 ml/minute) or mild hepatic impairment (PT <14 seconds), no change in dosage is necessary.

For patients with moderate renal impairment (GFR 10-30 ml/minute) or moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Insufficient data are available to support the use of venlafaxine in patients with severe renal impairment (GFR <10 ml/minute) or severe hepatic impairment (PT >18 seconds).

**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:**

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.3 and 4.8).

The efficacy and safety of venlafaxine 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 for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine has been shown to be efficacious during long-term (up to 12 months) treatment.

In clinical trials venlafaxine was demonstrated 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 sections 4.4 and 4.8). Following treatment with daily doses of venlafaxine greater than 75 mg 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 section 4.5).

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. Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder (see section 4.8).

This medicinal product contains lactose monohydrate. 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.

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). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 31% of patients treated with venlafaxine and in approximately 17% of placebo patients. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia 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 sections 4.2 and 4.4).

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.

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.

7. Significant electrocardiogram findings were observed in 0.8% of venlafaxine-treated patients compared with 0.7% of placebo-treated patients. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

8. Dose-related increases in blood pressure have been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200 mg (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 in post-marketing experience.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 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 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. In clinical trials the mean heart rate was increased 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 intra-ocular 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 in placebo-controlled trials. 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.

4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of 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 in combination with an MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine before starting an MAOI (see also section 4.3).

**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/depramine:** 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_{max} were increased by approximately 35%.

**Haloperidol:** In a pharmacokinetic study co-administration of venlafaxine with a single 2 mg oral dose of haloperidol resulted in a 42% decrease in renal clearance, a 70% increase in AUC and an 88% increase in C_{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 temporally 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.

**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 metabolisers. 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 is 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 is administered with cimetidine.

**Warfarin:** Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin following the addition of venlafaxine.

**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.

### 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 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 section 4.4.

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; **Rare**: prolonged bleeding time, haemorrhage, thrombocytopenia; **Very rare**: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see section 4.4) - **Common**: hypertension, palpitation, vasodilatation; **Uncommon**: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); **Very rare**: Torsade de Pointes, QT prolongation, ventricular tachycardia, 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 section 4.4), weight gain or loss; **Uncommon**: hyponatraemia including SIADH (see section 4.4), increased liver enzymes (see below); **Rare**: hepatitis; **Very rare**: prolactin increased.
Musculo-skeletal disorders - **Common**: arthralgia, myalgia; **Uncommon**: muscle spasm; **Very rare**: rhabdomyolysis.

Neurological disorders - **Very common**: dizziness, dry mouth, insomnia, nervousness, 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, dystonia, mania or hypomania (see section 4.4), neuroleptic malignant syndrome-like effects, seizures (see section 4.4), serotonergic syndrome; **Very rare**: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4).

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

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

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

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

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

**Adverse events from paediatric clinical trials:**

In pediatric 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 sections 4.2 and 4.4).

**Special Notes:**

In all premarketing depression trials with venlafaxine tablets, seizures were reported in 0.3% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in venlafaxine treated patients in clinical trials for depression and GAD. No seizures occurred in placebo-treated patients in depression studies. Seizures were reported in 0.2% of placebo-treated patients in GAD studies (see section 4.4).

Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with venlafaxine is 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 and serotonin syndrome and changes in level of consciousness 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: Nervous system, Psychoanaleptics, Antidepressants, Other antidepressants

ATC code: M03B X02

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, 0-desmethylvenlafaxine, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and 0-desmethylvenlafaxine reduce β-adrenergic responsiveness in animais 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 172 ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. 0-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and Odesmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak Odesmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and Odesmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and Odesmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. 0-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 225 mg/day.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Colloidal silica, anhydrous
Magnesium stearate
Sodium starch glycolate (Type A)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions.

6.5 Nature and contents of container
Transparent PVC/PVdC-aluminium blisters.
Blisters packs of 10, 20, 28, 30, 50, 56, 60 & 100 tablets. Hospital packs of 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0712
PL 0289/0716

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/10/2007

10 DATE OF REVISION OF THE TEXT

30/10/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains the equivalent of 50 mg of venlafaxine as 56.568 mg venlafaxine hydrochloride.

Excipients:
Each tablet contains 129.372 mg of lactose, monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Mottled peach, round, flat bevelled tablet, on one side scored and debossed “9” on one side of the score and “3” on the other side of the score. Debossed with “7381” on the opposite side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Venlafaxine is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response venlafaxine is 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 should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75 mg per day given in two divided doses (37.5 mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine be taken with food.

If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150 mg per day given in two divided doses (75 mg 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 75 mg 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 375 mg per day. The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited number of tablets 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 sections 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:**

For patients with mild renal impairment (GFR>30 ml/minute) or mild hepatic impairment (PT<14 seconds), no change in dosage is necessary.

For patients with moderate renal impairment (GFR 10-30 ml/minute) or moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Insufficient data are available to support the use of venlafaxine in patients with severe renal impairment (GFR<10 ml/minute) or severe hepatic impairment (PT>18 seconds).

**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:**

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.3 and 4.8).

The efficacy and safety of venlafaxine 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 for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine has been shown to be efficacious during long-term (up to 12 months) treatment.

In clinical trials venlafaxine was demonstrated 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 sections 4.4 and 4.8). Following treatment with daily doses of venlafaxine greater than 75 mg 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 section 4.5).

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. Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder (see section 4.8).
This medicinal product contains lactose monohydrate. 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.

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). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 31% of patients treated with venlafaxine and in approximately 17% of placebo patients. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia 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 sections 4.2 and 4.4).

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.

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.

7. Significant electrocardiogram findings were observed in 0.8% of venlafaxine-treated patients compared with 0.7% of placebo-treated patients. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

8. Dose-related increases in blood pressure have been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200 mg (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 in post-marketing experience.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 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 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. In clinical trials the mean heart rate was increased 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 intra-ocular 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 in placebo-controlled trials. 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 vanlafaxine should not be used in combination with SSRIs unless clinically indicated and on the advice of a specialist.

4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of 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 in combination with an MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine before starting an MAOI (see also section 4.3).

**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/depramine:** 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 2 mg 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 temporally 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.

**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 metabolisers. 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 is 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 is administered with cimetidine.

**Warfarin:** Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin following the addition of venlafaxine.

**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.

### 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 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 section 4.4.

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; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see section 4.4) - Common: hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, 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 section 4.4), weight gain or loss; Uncommon: hyponatraemia including SIADH (see section 4.4), increased liver enzymes (see below); Rare: hepatitis; Very rare: prolactin increased.
Musculo-skeletal disorders - **Common**: arthralgia, myalgia; **Uncommon**: muscle spasm; **Very rare**: rhabdomyolysis.

Neurological disorders - **Very common**: dizziness, dry mouth, insomnia, nervousness, 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, dystonia, mania or hypomania (see section 4.4), neuroleptic malignant syndrome-like effects, seizures (see section 4.4), serotonergic syndrome; **Very rare**: delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia (see section 4.4).

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

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

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

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

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

**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 sections 4.2 and 4.4).

**Special Notes:**

In all premarketing depression trials with venlafaxine tablets, seizures were reported in 0.3% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in venlafaxine treated patients in clinical trials for depression and GAD. No seizures occurred in placebo-treated patients in depression studies. Seizures were reported in 0.2% of placebo-treated patients in GAD studies (see section 4.4).

Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with venlafaxine is 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 and serotonin syndrome and changes in level of consciousness 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:** Nervous system, Psychoanaleptics, Antidepressants, Other antidepressants

**ATC code:** M03B X02

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 172 ng/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 Odesmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and Odesmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and Odesmethylvenlafaxine 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 225 mg/day.
6  PHARMACEUTICAL PARTICULARS

6.1  List of excipients
Lactose monohydrate
Colloidal silica, anhydrous
Magnesium stearate
Sodium starch glycolate (Type A)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2  Incompatibilities
Not applicable

6.3  Shelf life
3 years

6.4  Special precautions for storage
No special storage conditions.

6.5  Nature and contents of container
Transparent PVC/PVdC-aluminium blisters.
Blister packs of 28, 30, 42, 56, 60 & 100 tablets. Hospital packs of 50 tablets.
Not all pack sizes may be marketed.

6.6  Special precautions for disposal
No special requirements

7  MARKETING AUTHORISATION HOLDER
TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8  MARKETING AUTHORISATION NUMBER(S)
PL 00289/0713
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/10/2007

10 DATE OF REVISION OF THE TEXT

30/10/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 75 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains the equivalent of 75 mg of venlafaxine as 84.852 mg venlafaxine hydrochloride.

Excipients:
Each tablet contains 194.058 mg of lactose, monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
Mottled peach, round, flat bevelled tablet, on one side scored and debossed “9” on one side of the score and “3” on the other side of the score. Debossed with “7382” on the opposite side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Venlafaxine is indicated for the treatment of major depressive disorder including depression accompanied by anxiety. All patients should be evaluated for the risk of suicidality and monitored for clinical worsening (see sections 4.2 and 4.4).

Following an initial response venlafaxine is 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 should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75 mg per day given in two divided doses (37.5 mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine be taken with food.

If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150 mg per day given in two divided doses (75 mg 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 75 mg 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 375 mg per day. The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited number of tablets 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 sections 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:**

For patients with mild renal impairment (GFR>30 ml/minute) or mild hepatic impairment (PT<14 seconds), no change in dosage is necessary.

For patients with moderate renal impairment (GFR 10-30 ml/minute) or moderate hepatic impairment (PT 14-18 seconds), the dose should be reduced by 50%. This dose may be given once daily due to longer half-lives of venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Insufficient data are available to support the use of venlafaxine in patients with severe renal impairment (GFR<10 ml/minute) or severe hepatic impairment (PT>18 seconds).

**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:**

Controlled clinical studies in children and adolescents with Major Depressive Disorder failed to demonstrate efficacy and do not support the use of venlafaxine in these patients (see sections 4.3 and 4.8).

The efficacy and safety of venlafaxine 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 for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine has been shown to be efficacious during long-term (up to 12 months) treatment.

In clinical trials venlafaxine was demonstrated 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 sections 4.4 and 4.8). Following treatment with daily doses of venlafaxine greater than 75 mg 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 section 4.5).

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. Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder (see section 4.8).

This medicinal product contains lactose monohydrate. 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.

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). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 31% of patients treated with venlafaxine and in approximately 17% of placebo patients. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia 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 sections 4.2 and 4.4).

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.

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.

7. Significant electrocardiogram findings were observed in 0.8% of venlafaxine-treated patients compared with 0.7% of placebo-treated patients. Significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

8. Dose-related increases in blood pressure have been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200 mg (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 in post-marketing experience.

9. Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine 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 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. In clinical trials the mean heart rate was increased 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 intra-ocular 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 in placebo-controlled trials. 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.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

**MAOIs:** Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of 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 in combination with an MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine before starting an MAOI (see also section 4.3).

**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/depramine:** 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 2 mg 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 temporally 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.

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 metabolisers. 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 is 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 is administered with cimetidine.

Warfarin: Potentiation of anticoagulant effects including increases in PT or INR have been reported in patients taking warfarin following the addition of venlafaxine.

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.

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 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 section 4.4.

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; Rare: prolonged bleeding time, haemorrhage, thrombocytopenia; Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (see section 4.4) - Common: hypertension, palpitation, vasodilatation; Uncommon: hypotension/postural hypotension, syncope, arrhythmias (including tachycardia); Very rare: Torsade de Pointes, QT prolongation, ventricular tachycardia, 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 section 4.4), weight gain or loss; **Uncommon:** hyponatraemia including SIADH (see section 4.4), increased liver enzymes (see below); **Rare:** hepatitis; **Very rare:** prolactin increased.

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

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

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

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

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

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

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

**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 sections 4.2 and 4.4).

**Special Notes:**

In all premarketing depression trials with venlafaxine tablets, seizures were reported in 0.3% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in venlafaxine treated patients in clinical trials for depression and GAD. No seizures occurred in placebo-treated patients in depression studies. Seizures were reported in 0.2% of placebo-treated patients in GAD studies (see section 4.4).

Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with venlafaxine is 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 and serotonin syndrome and changes in level of consciousness have been reported in association with overdosage of venlafaxine usually when in combination with alcohol and/or other CNS drugs.

Management of Overdose - 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: Nervous system, Psychoanaleptics, Antidepressants, Other antidepressants

ATC code: M03B X02

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, 0-desmethylvenlafaxine, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and 0-desmethylvenlafaxine reduce J3-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 172 ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. 0-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. 0-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 225 mg/day.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Colloidal silica, anhydrous
Magnesium stearate
Sodium starch glycolate (Type A)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions.

6.5 Nature and contents of container
Transparent PVC/PVdC-aluminium blisters.
Blister packs of 20, 28, 30, 50, 56, 60 & 100 tablets. Hospital packs of 50 & 500 (10x50) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England
8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0714
PL 00289/0718

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/10/2007

10 DATE OF REVISION OF THE TEXT
30/10/2007
PATIENT INFORMATION LEAFLET

VENLAFAXINE 25, 37.5, 50 and 75 mg TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- This leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

1. Venlafaxine: what it is and what it’s used for
2. Before you take Venlafaxine
3. How to take Venlafaxine
4. Possible side effects
5. Storing Venlafaxine.

The name of your medicine is Venlafaxine 25, 37.5, 50 or 75 mg Tablets.

- The active ingredient is venlafaxine hydrochloride.
- The other ingredients are lactose monohydrate, sodium starch glycolate, colloidal silica, magnesium stearate, yellow iron oxide and red iron oxide.

The Marketing Authorisation holder and company responsible for manufacture is TEVA UK Limited, Eastbourne, BN22 9AG.

1 VENLAFAXINE: WHAT IT IS AND WHAT IT’S USED FOR

- Each tablet contains 25, 37.5, 50 or 75 mg of venlafaxine (as hydrochloride). Venlafaxine belongs to a group of drugs called antidepressants.
- The 25 mg tablets are available in pack sizes of 30 and 60 tablets.
- The 37.5 mg tablets are available in pack sizes of 10, 20, 28, 30, 50, 56, 60 and 100 tablets.
- The 50 mg tablets are available in pack sizes of 28, 30, 42, 56, 60 and 100 tablets.
- The 75 mg tablets are available in pack sizes of 20, 28, 30, 50, 56, 60 and 100 tablets.
- Hospital packs are available in a pack size of 50 tablets. The 75 mg tablets are also available in a hospital pack size of 500 tablets.

- Not all pack sizes may be marketed.
- Your medicine is used to treat the symptoms of depression, including depression accompanied by anxiety.
- Venlafaxine is an antidepressant which belongs to a group of medicines called serotonin-norepinephrine reuptake inhibitors (SNRIs). It is believed that people who are depressed could have lower levels of serotonin and norepinephrine in their brain. Venlafaxine increases the levels of these substances in the brain and therefore may help to relieve the symptoms of depression.
- Venlafaxine may continue to be prescribed to you by your doctor, even if you are feeling better, in order to prevent your symptoms from returning or to prevent you from becoming depressed in the future.

2 BEFORE YOU TAKE VENLAFAXINE

Do NOT take Venlafaxine if you:
- Are allergic (hypersensitive) to venlafaxine or any of the other ingredients of this medicine.
- Are taking or have recently taken (within the last two weeks) another antidepressant drug known as a monoamine oxidase inhibitor (MAOI), e.g. phenelzine.
- Have heart problems or high blood pressure.
- Have been told by your doctor that you have an imbalance of blood in the body.
- Are under the age of 18.

Talk to your doctor before taking Venlafaxine if:
- You have suffered from or have a history of mania (periods of unusually elevated mood and activity).
- You have a history of epilepsy or heart disease.
- You have a history of bleeding disorders or a tendency to bleed.
- You have liver or kidney disease, as your dose of Venlafaxine may need to be lower.
- You have eye problems, raised pressure in the eye or suffer from or have a history of narrow angle glaucoma.
- You have high cholesterol.
- You are taking any other antidepressant drugs, e.g. imipramine, fluoxetine, paroxetine or lithium.
- You are taking cimetine (drug used for stomach ulcers), especially if you are elderly.
- You are taking drugs for migraine known as triptans, e.g. sumatriptan.
- You are taking tablets that thin the blood, e.g. warfarin.
- You are taking haloperidol, clozapine or other drugs for schizophrenia.
- You are taking ketoconazole (used for fungal infections) or erythromycin (an antibiotic).
- You are taking medication to help you lose weight (e.g. phentermine).
- You are taking or have recently taken any other medicines.
- You are due to receive electroconvulsive therapy (ECT).

Pregnancy and Breastfeeding:
- If you are pregnant or become pregnant you should only take Venlafaxine if it is clearly needed. Your doctor should have discussed this with you. If not, ask your doctor or pharmacist for advice before taking any medicine.
- If you are planning to become pregnant, or are breast-feeding, consult your doctor before taking Venlafaxine.

Important information about some of the ingredients of your medicine.
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Driving or using machinery:
- Venlafaxine may impair your judgement and co-ordination. Do not drive or operate machinery if you think you are affected.

Alcohol should be avoided while taking Venlafaxine.

3 HOW TO TAKE VENLAFAXINE

Your doctor has decided the dose which is suited to you. Always follow your doctor's instructions and those which are on the pharmacy label. If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist.

You should swallow your tablets whole with a drink of water, at mealtimes.

The usual starting dose is one 37.5 mg tablet twice a day, one in the morning and one in the evening. However your doctor may prescribe a different dose for you depending on your condition. The maximum daily dose should not exceed 375 mg a day.

It may take several days or more before your medicine has any effect. This is quite normal.

Thoughts of self-harm:
- People who suffer from anxiety disorders and/or who are depressed can sometimes have thoughts of killing or harming themselves. These thoughts may be increased when you begin to start taking antidepressants, as these medicines all take time to work.

These thoughts are more likely if you:
- Are a young adult, e.g. aged 16-29.
- Have previously had thoughts about harming or killing yourself.

If you have these thoughts, contact your hospital or doctor straight away.
You may need to take Venlafaxine for several months during which time your doctor will monitor your condition. If it is necessary to discontinue treatment then this should not be done without your doctor’s advice, even if you feel better. Your doctor will ask you to reduce your dose gradually before stopping treatment altogether. When you stop taking Venlafaxine you may experience some of the following common side effects: dizziness, tingling or numbness, sleeplessness, nightmares, agitation or anxiety, feeling or being sick, tremor, sweating, headaches, diarrhoea, palpitations or feeling emotional. You may also experience additional side effects: hypomania (feeling ‘high’ or over excited), nervousness, mental confusion, tiredness, sleeplessness, vertigo, fits, tinnitus (ringing in the ears), dry mouth or loss of appetite.

Children under 16 years of age
Venlafaxine is not recommended for use in children or adolescents under 18 years of age.

If you take more Venlafaxine than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Overdose of Venlafaxine (usually when in combination with alcohol or other central nervous system (CNS) drugs) can cause changes in heart rhythm, fits, low blood pressure, vertigo (a sensation that your surroundings are spinning either up and down or from side to side) and changes in the level of consciousness. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Venlafaxine
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

Your doctor may wish to monitor your blood pressure while you are taking Venlafaxine.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Venlafaxine can have side effects. A few people may develop the following rare, but very serious side effects. If you experience any of the following symptoms, you should tell your doctor immediately or go to the casualty department at your nearest hospital:
- Swelling of the lips, face and neck leading to severe difficulty in swallowing or breathing
- A high temperature with rigid muscles, confusion, agitation or sweating or jerky muscle movements which you cannot control
- Mania or hypomania (feeling ‘high’ or over excited), fits
- Aggression
- Restlessness and needing to move often, with a feeling of not being able to sit or stand still.

The following side effects have also been reported at the approximate frequencies shown. Very common (affecting more than one person in 10):
- Headache, dizziness
- Constipation
- Feeling sick
- Dry mouth, nervousness, sweating (especially night sweats)
- Loss of strength, sleepiness
- Difficulty sleeping
- Abnormal ejaculation/orgasm, inability to achieve orgasm or erectile dysfunction (impotence).

Common (affecting fewer than one person in 10 but more than one person in 100):
- Breathlessness
- Tinnitus (ringing in the ears)
- Rashes, itching
- Dilation of the pupils, blurred vision
- Weight gain or loss
- Joint or muscle pains
- Anxiety, confusion, agitation, tremors, nightmares
- Flushing, palpitations
- Abnormal muscle rigidity, yawning
- Loss of sensation in the extremities, pins and needles
- Increased desire to urinate
- Stomach pains, indigestion, heartburn, being sick, diarrhoea
- High or low temperature
- High blood pressure, chills
- Loss of sexual desire
- Abnormal periods in women
- Loss of appetite.

Uncommon (affecting fewer than one person in 100 but more than one person in 1000):
- Bruise-like discolouration of the skin
- Bleeding from the nose or mouth or genitals
- Excessive loss of blood during menstruation
- Dizziness on standing
- Fainting
- Increase or decrease in heart rate
- Clenching or grinding of the teeth
- Hair loss
- Sensitivity to light
- Altered taste sensations
- Hallucinations
- Inability to urinate.

Rare (affecting fewer than one person in 1000 but more than one person in 10,000):
- Unusual bleeding, bruising or prolonged bleeding times
- Gastrointestinal bleeding (black, tarry stools)
- Poor muscular co-ordination, speech disorders
- Severe rashes or blisters of the lips, eyes, nose, mouth or genitals
- Excessive or spontaneous flow of milk from the mammary glands
- Inflammation of the liver (hepatitis)
- Saininosis
- Periods of unusually elevated high or low mood and activity
- Neuroleptic malignant syndrome-like effects (reaction to certain drugs for psychiatric conditions e.g. fever, muscle rigidity, altered mental status and problems with the nervous system.

Very rare (affecting fewer than one person in 10,000):
- Anaemia
- Blood disorders
- Heart problems
- Wasting of the muscles
- Mental confusion
- Inability to sit still
- Pancreatitis (nausea, vomiting, abdominal pain and back pain).

Venlafaxine sometimes causes side effects which you may not be aware of, such as increases in blood pressure, abnormal heart beat, changes in blood levels of liver enzymes, sodium and cholesterol. It can also produce changes in the composition of the blood, therefore your doctor may wish to monitor these effects by doing various tests, especially if you have been taking Venlafaxine for a long time.

If you notice these or any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5 STORING VENLAFAXINE

Keep Venlafaxine out of the reach and sight of children. There are no special storage instructions. Do not transfer to another container. Do not use Venlafaxine after the expiry date shown on the outer packaging. Return all unused medicines to your pharmacist for safe disposal.

Revised: May 2007

TEVA UK Limited 68995-T
Each tablet contains 25 mg Venlafaxine (as hydrochloride). Also includes lactose.

**Dosage:**
Use as directed by the physician. Please read the enclosed package leaflet before use.

**Keep Out of the Reach and Sight of Children.**

There are no special storage instructions.
Each tablet contains 25 mg Venlafaxine (as hydrochloride). Also includes lactose.

**Dosage:**
Use as directed by the physician. Please read the enclosed package leaflet before use.

**Keep Out of the Reach and Sight of Children.**

There are no special storage instructions.

Venlafaxine 25 mg Tablets
Venlafaxine hydrochloride
Oral Use
30 Tablets
Each tablet contains 50 mg Venlafaxine (as hydrochloride). Also includes lactose.

**Dosage and Administration**
Use as directed by the physician. Please read the enclosed package leaflet before use.

**Keep Out of the Reach and Sight of Children.**
There are no special storage instructions.