Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets
(venlafaxine hydrochloride)
PL 17907/0250-1

UK Public Assessment Report

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Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets
(venlafaxine hydrochloride)

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Venlafaxine 37.5 mg and 75 mg Tablets (PL 17907/0250-1) on 24th February 2011. These are prescription-only medicines (POM).

Venlafaxine tablets contain the active ingredient venlafaxine, as venlafaxine hydrochloride. Venlafaxine belongs to the class of medicines called ‘antidepressants’ which are used to relieve the symptoms of depressive illness and any associated anxiety.

People who are depressed may have lower levels than usual of substances called ‘serotonin’ and ‘noradrenaline’ in their brain. While it is not fully understood how antidepressants work, venlafaxine may help by increasing the levels of these substances in your brain.

The test products were considered to be generic versions of the UK reference products Efexor 37.5 mg and 75 mg tablets (PL 00011/0199 and 0201, John Wyeth and Brother Limited) based on the data submitted by Bristol Laboratories Limited.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Venlafaxine 37.5 mg and 75 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets
(venlafaxine hydrochloride)

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Venlafaxine 37.5 mg and 75 mg Tablets (PL 17907/0250-1) on 24th February 2011. These are prescription-only medicines (POM).

These are generic applications for Venlafaxine 37.5 mg and 75 mg Tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the innovator UK products, Efexor 37.5 mg and 75 mg tablets (PL 00011/0199 and 0201), authorised to John Wyeth and Brother Limited on 27th and 22nd November 1994 respectively. The innovator products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Venlafaxine 37.5 mg and 75 mg Tablets are 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. Following an initial response, Venlafaxine 37.5 mg and 75 mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

Venlafaxine hydrochloride 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 hydrochloride antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Pre-clinical 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. Its potency in inhibiting serotonin reuptake is approximately 5 times that of its noradrenaline reuptake inhibitory activity. 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 and receptor binding. Venlafaxine does not possess monoamine oxidase (MAO) inhibitor activity. In-vitro studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

Excretion of venlafaxine and its metabolites is primarily by the renal route, with only 4.7% of an administered dose appearing in urine as unchanged drug. The elimination half-life of venlafaxine is approximately 4 hours and that of O-desmethylvenlafaxine about 10 hours.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Venlafaxine 75 mg Tablets, to that of the reference product, Efexor 75 mg tablets (John Wyeth and Brother Limited). The
bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Venlafaxine hydrochloride

Nomenclature:

INN: Venlafaxine hydrochloride
Chemical name: (+) 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride

Structure:

Molecular formula: C_{17}H_{27}NO_{2}, HCl
Molecular weight: 313.9 g/mol
CAS No: 99300-78-4
Physical form: White or almost white powder
Solubility: Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone

The active substance, venlafaxine hydrochloride, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of venlafaxine hydrochloride are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of venlafaxine hydrochloride for inclusion in these medicinal products.
MEDICINAL PRODUCT

Description and Composition
Venlafaxine 37.5 mg and 75 mg Tablets are presented as peach-coloured, circular tablets, each containing 37.5 mg or 75 mg of the active ingredient, venlafaxine, as venlafaxine hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, lactose monohydrate, sodium starch glycollate, pregelatinised starch, magnesium stearate and yellow iron oxide (E172) and red iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of the colourants, yellow iron oxide (E172) and red iron oxide (E172), which comply with the requirements of the US Pharmacopoeia National Formulary (USPNF) and with the EU colouring regulation 95/45/EC. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate used has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Efexor 37.5 mg and 75 mg tablets (PL 00011/0199 and 0201, John Wyeth and Brother Limited).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

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

In-process controls have been provided and are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

Finished product specifications
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are
compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
Venlafaxine 37.5 mg and 75 mg Tablets are licensed for marketing in polyvinylchloride (PVC) / aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 28 or 56 tablets.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 2 years, with the storage instructions ‘Do not store above 25°C. Store in the original package’.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**
The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user testing report has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

**Conclusion**
All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Venlafaxine 37.5 mg and 75 mg Tablets from a pharmaceutical point of view.
PRE-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Venlafaxine 37.5 mg and 75 mg Tablets, products claiming to be generic medicinal products of Efexor 37.5 mg and 75 mg tablets (PL 00011/0199 and 0201, John Wyeth and Brother Limited).

No new pre-clinical data have been supplied with these applications and none are required for applications of this type.

A pre-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
CLINICAL ASSESSMENT

INDICATIONS
Venlafaxine 37.5 mg and 75 mg Tablets are 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. Following an initial response, Venlafaxine 37.5 mg and 75 mg Tablets are indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
The toxicology of venlafaxine hydrochloride is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The clinical pharmacology of venlafaxine hydrochloride is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - Bioequivalence study
The applications are supported by a bioequivalence study comparing the pharmacokinetic profiles of Venlafaxine 75 mg Tablets (test) and Efexor 75 mg tablets - John Wyeth and Brother Limited (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

This was a comparative, randomised, open-label, two-treatment, two-period, two-sequence, single-dose crossover bioequivalence study conducted in 30 healthy, adult human male subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 10 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 48.0 hours after administration of test or reference product. Plasma levels of venlafaxine hydrochloride and the O-desmethyl metabolite were detected by a validated LC-MS/MS analytical method.
The primary pharmacokinetic parameters for this study were \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \).

**Results**

30 subjects were enrolled in the study; 20 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation and non-inclusion in the pharmacokinetic analysis of 10 subjects was satisfactorily justified.

**Safety** - There were 20 adverse events reported during the study period by 15 fifteen subjects, none were considered serious. There was an equal distribution of adverse events between test and reference products. There were no clinically significant changes in the post-study evaluations of haematology and biochemistry. There were no deaths or serious or significant adverse events.

A summary of the results of the bioequivalence study is tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean Ratio (Y/X) %</th>
<th>90% CI (Parametric)</th>
</tr>
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<tbody>
<tr>
<td><strong>Venlafaxine hydrochloride</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>97.68</td>
<td>86.34-110.51%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng.h/ml)</td>
<td>100.51</td>
<td>89.36-113.05%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng.h/ml)</td>
<td>100.11</td>
<td>89.39-112.11%</td>
</tr>
<tr>
<td><strong>O-desmethylvenlafaxine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>95.93</td>
<td>90.11-102.12%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng.h/ml)</td>
<td>98.52</td>
<td>93.49-103.83%</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng.h/ml)</td>
<td>97.99</td>
<td>93.00-103.26%</td>
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\( C_{\text{max}} \) maximum plasma concentration
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) for venlafaxine hydrochloride and its metabolite, O-desmethylvenlafaxine, fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.
Satisfactory justification is provided for a bio-waiver for Venlafaxine 37.5 mg Tablets. As Venlafaxine 37.5 mg and 75 mg Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 75 mg strength can be extrapolated to the 37.5 mg strength tablets.

**EFFICACY**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of venlafaxine hydrochloride is well-established from its extensive use in clinical practice.

**SAFETY**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of venlafaxine hydrochloride is well-known.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics**

The approved SmPCs are consistent with those for the reference products and are acceptable.

**Patient Information Leaflet**

The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user testing has been evaluated and is accepted.

**Labelling**

The labelling is satisfactory.

**Clinical overview**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**CONCLUSIONS**

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Venlafaxine 37.5 mg and 75 mg 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.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Venlafaxine 75 mg Tablets, and the UK reference product, Efexor 75 mg tablets (John Wyeth and Brother Limited).

As the proposed products, Venlafaxine 37.5 mg and 75 mg Tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 75 mg strength were extrapolated to the 37.5 mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the reference products and are satisfactory.

A mock-up PIL has been provided. The PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended). The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence studies and their conclusions support the claim that the applicant’s Venlafaxine 37.5 mg and 75 mg Tablets are generic versions of the reference products, Efexor 37.5 mg and 75 mg tablets (John Wyeth and Brother Limited). Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
VENLAFAXINE 37.5 mg Tablets
VENLAFAXINE 75 mg Tablets

(venlafaxine hydrochloride)

PL 17907/0250-1

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the marketing authorisation applications on 3rd July 2009

2  Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th July 2009

3  Following assessment of the applications the MHRA requested further information relating to the quality dossier on 8th December 2009 and 7th September 2010

4  The applicant responded to the MHRA’s requests, providing further information for the quality sections on 6th September 2010 and 15th December 2010 respectively

5  The applications were determined on 24th February 2011
Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets

(venlafaxine hydrochloride)

PL 17907/0250-1

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Venlafaxine 37.5 mg and 75 mg Tablets (PL 17907/0250-1) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Venlafaxine 37.5 mg Tablets.
Venlafaxine 75 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 37.5 / 75 mg of Venlafaxine as Venlafaxine Hydrochloride Ph.Eur. as the active substance.
Each tablet contains approximately 52 / 104 mg of Lactose Monohydrate.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Peach coloured, round tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Major depressive disorder
Venlafaxine tablets 37.5 / 75 mg are 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.
Following an initial response Venlafaxine tablets 37.5 / 75 mg 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 tablets 37.5 / 75 mg should not be started until 14 days after discontinuing a monoamine oxidase inhibitor (MAOI).

Depression:
The recommended dose is 75mg per day given in two divided doses (37.5 mg twice daily). Most patients respond to this dose. It is recommended to take Venlafaxine tablets 37.5 / 75 mg with food.

If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 375 mg per day. 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 hospitalized patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg with an interval not less than 4 days until the desired response is achieved.

The dose should then be gradually reduced, to the minimum effective dose consistent with patient response and tolerance. A limited amount of Venlafaxine should be provided to reduce the risk from overdose.

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.
UKPAR Venlafaxine 37.5 mg & 75 mg Tablets

Anti-depressive medicinal products should continue for at least 6 months following remission.

**Patients at increased risk for suicide:**
Patients with increased risk factors for suicide should be carefully evaluated for the presence or worsening of suicide-related behaviour 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 with glomerular filtration rate (GFR between 30-70ml/minute) or mild hepatic impairment (PT <14 seconds), no change in dosage is necessary but caution is advised.

For patients that require haemodialysis and in patients with severe renal impairment (GFR <30ml/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 the longer half-lives of Venlafaxine and O-desmethylvenlafaxine (ODV) in these patients.

Because of inter-individual variability in clearance in these patients, individualization of dosage may be desirable.

**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, the potential for changes in neurotransmitter sensitivity and affinity occurring with aging. See also dosage recommendations for renal impairment). Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown. The lowest effective dose should always be used and patients should be carefully monitored when an increase in the dose is required.

**Children/Adolescents under 18 years of age:**
Venlafaxine is not recommended for use in children and adolescents under 18 years of age. Also patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behavior and anger) when they take this class of medicines. Also, the long-term safety concerning growth, maturation and development of the brain in this age group have not yet been demonstrated.

**Maintenance/Continuation/Extended Treatment:**
The physician should periodically re-evaluate the usefulness of long-term treatment with Venlafaxine tablets **37.5 / 75** mg for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Venlafaxine tablets **37.5 / 75** mg 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 section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). Following treatment with daily doses of venlafaxine greater than 75mg for more than one week, it is recommended that when discontinuing treatment the dose should be gradually reduced over at least a further week. If high doses have been used for more than 6 weeks tapering over at least a 2 week period is recommended. If intolerable symptoms occur following a decrease in the dose or upon
discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Route of administration: oral

It is recommended to take venlafaxine tablets with food, at approximately the same time each day.

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

4.3 Contraindications
1. Known hypersensitivity to venlafaxine or any of the excipients.
2. Concomitant use of venlafaxine with monoamine oxidase inhibitors is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Venlafaxine tablets must be discontinued for at least 7 days before starting treatment with an irreversible MAOI (see sections 4.4 and 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.
4. Venlafaxine tablets 37.5/75 mg should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder.

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

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

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

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

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
Use in children and adolescents under 18 years of age:
Venlafaxine should not be used in the treatment of children and adolescents under 18 years of age. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with anti-depressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Elderly patients:
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

2. Withdrawal symptoms seen on discontinuation of venlafaxine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 35% of patients treated with venlafaxine and in approximately 17% of patients taking placebo. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia 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.

3. Mania or hypomania:
Mania or hypomania has been reported rarely in patients who have received antidepressants, including venlafaxine. As with all antidepressants, Venlafaxine tablets 37.5 / 75 mg should be used with caution in patients with a history or family history of bipolar disorder.

4. Aggression:
Treatment with venlafaxine (especially during initiating and discontinuing treatment and change in the dose) has been associated with reports of aggression.

5. Psychomotor restlessness (Akathisia):
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 has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients. In post marketing experience, fatal cardiac arrhythmias have been reported with use of venlafaxine, especially in overdose. The balance of risks and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia.
7. Heart rate:
Increases in heart rate can occur, particularly with higher doses. Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate. 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:
Increase in blood pressure has been reported commonly from clinical trials, particularly in patients receiving daily doses greater than 200mg (see section 4.8). Sustained increases of blood pressure could have adverse consequences. Periodic measurement of blood pressure is therefore recommended for patients receiving venlafaxine after initiation of treatment and change in dose. 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. Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function.

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

9. Seizures (convulsions):
Seizures are a potential risk with antidepressant drugs, especially in overdose. Venlafaxine tablets 37.5 / 75 mg 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 tablets 37.5 / 75 mg should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored.

10. 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. Increased heart rate:
Increase 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. Hyponatraemia (syndrome of Inappropriate Antidiuretic Hormone (SIADH)):
Cases of hyponatraemia secretion may occur with venlafaxine. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise volume-depleted may be at greater risk for this event.

13. Mydriasis (Narrow angle glaucoma):
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.

14. Abnormal bleeding:
Medicinal products that inhibit serotonin uptake may lead to reduced platelet function. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking venlafaxine. As with other serotonin-reuptake inhibitors, venlafaxine should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.
15. Serum cholesterol:
Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

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

17. 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.

18. Serotonin syndrome:
As with other serotonergic agents, serotonin syndrome, potentially life threatening condition may occur with venlafaxine treatment, particularly with concomitant use of other agents, such as MAOIs, that may affect the serotonergic neurotransmitter systems. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

19. Lactose intolerance:
These tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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, and when an MAOI is initiated soon after discontinuation of venlafaxine. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Do not use Venlafaxine tablets 37.5 / 75 mg in combination with a MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Venlafaxine tablets 37.5 / 75 mg before starting an MAOI.

Serotonergic drugs: Based on the known mechanism of action of venlafaxine and the potential for serotonergic syndrome, concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, tramadol, or St. John’s Wort (Hypericum perforatum)), with medicinal agents which impair metabolism of serotonin (including MAOIs), or with serotonin precursors (such as tryptophan supplements).

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

Effect of venlafaxine on other medicinal products:

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

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

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

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

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

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

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

**Cimetidine:** Cimetidine inhibits 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 tablets 37.5 / 75 mg 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 tablets 37.5 / 75 mg is administered with cimetidine.

**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 tablets 37.5 / 75 mg.

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

**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.

**Effect of other medicinal products on venlafaxine:**

**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).

4.6 Pregnancy and lactation

Venlafaxine tablets 37.5 / 75 mg 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. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with Venlafaxine Tablets taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

**Lactation:**

There is evidence to suggest that venlafaxine and its metabolite, ODV, are excreted in breast milk. A risk to sucking child cannot be excluded. 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

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, gastrointestinal haemorrhage

*Not known:* blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia), thrombocytopenia, mucous membrane bleeeing, prolonged bleeding time,

**Cardiovascular and vascular disorders** –

*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, weight loss

**Uncommon:** hyponatraemia including SIADH, increased liver enzymes, weight gain

**Not known:** abnormal liver function tests, hyponatraemia, hepatitis, SIADH, increased prolactin

**Musculo-skeletal disorders**

**Not known:** rhabdomyolysis.

**Neurological disorders**

**Very common:** dry mouth, headache

**Common:** abnormal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor

**Uncommon:** apathy, hallucinations, myoclonus

**Rare:** ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, mania or hypomania.

**Not known:** neuroleptic malignant syndrome-like effects, seizures, serotonergic syndrome delirium, extrapyramidal disorders including dyskinesia and dystonia, tardive dyskinesia, psychomotor restlessness/akathisia.

**Renal and urinary disorders**

**Common:** urinary frequency

**Uncommon:** urinary retention.

**Reproductive and breast disorders**

**Very common:** anorgasmia, erectile dysfunction, abnormal ejaculation/orgasm

**Common:** decreased libido, impotence, menstrual cycle disorders

**Uncommon:** menorrhagia

**Rare:** galactorrhoea.

**Respiratory system disorders**

**Common:** dyspnoea, yawning

**Very rare:** pulmonary eosinophilia.

**Skin and subcutaneous tissue disorders**

**Very common:** sweating (including night sweats)

**Uncommon:** pruritus, rash, alopecia

**Not known:** erythema multiforme, Stevens Johnson syndrome.

**Special senses**

**Common:** abnormal vision/ accommodation, mydriasis, tinnitus
Uncommon: altered taste sensation.

Not known: angle closure glaucoma.

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

Withdrawal symptoms seen on discontinuation of venlafaxine treatment
Discontinuation of venlafaxine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and abnormal dreams), agitation or anxiety, nausea and/or vomiting, tremor, sweating, headache, diarrhoea, palpitations and emotional instability are the most commonly reported withdrawal reactions. Additional withdrawal reactions include hypomania, nervousness, confusion, fatigue, somnolence, convulsion, vertigo, tinnitus, dry mouth and anorexia. Generally these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

Special Notes:
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 tablets-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.

Nausea is most common at the start of treatment with the incidence decreasing over the first few weeks. The nausea experienced with Venlafaxine tablets 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.

Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation.

4.9 Overdose
In post marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicinal products. The most commonly reported events in overdose include tachycardia, changes in level of consciousness ranging from somnolence to coma, mydriasis, convulsion, and vomiting.

Other reported events include Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia and hypotension, vertigo, serotonin syndrome

Management of Over dosage - 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

**ATC Code: NO6AX16 Group: ANTIDEPRESSANT**

Venlafaxine tablets are 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 tablets’ 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 and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, H₁, histaminergic or α₁ 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.

Venlafaxine do not possess monoamine oxidase (MAO) inhibitor activity.

*In-vitro* studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

5.2 Pharmacokinetic properties

Venlafaxine is well absorbed and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 ± 7 and 11 ± 12 hours respectively. Mean peak O-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

5.3 Preclinical safety data

Studies with venlafaxine in rats and mice revealed no evidence of carcinogenesis. Venlafaxine was not mutagenic in a wide range of *in vitro* and *in vivo* tests.
Reduced fertility was observed in a study in which both male and female rats were exposed to the major metabolite of venlafaxine (ODV). This exposure was approximately 1 to 2 times that of a human dose of 375mg/day of venlafaxine. The human relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
The active constituent is venlafaxine as hydrochloride. Other constituents are microcrystalline cellulose, lactose monohydrate, sodium starch glycollate, pregelatinised starch, magnesium stearate and yellow iron oxide (E172) and red iron oxide (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
PVC /Aluminium foil blisters of 28 or 56 tablets.

6.6 Special precautions for disposal
None.

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
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PL 17907/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
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UKPAR Venlafaxine 37.5 mg & 75 mg Tablets
PL 17907/0250-1

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR USER

Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets
Venlafaxine Hydrochloride

Important things you need to know about Venlafaxine
- Venlafaxine is for depression
- Venlafaxine should not be given to anyone under 18 years of age—see section 3 'Children and adolescents under 18 years of age'
- Venlafaxine may not work straight away. After you start treatment, you may feel worse before you feel better. It may take between two to four weeks before you start feeling better. Tell your doctor if you do not feel better—see section 2 'You may feel worse before you feel better'.
- Some people who are depressed may think of harming or killing themselves. If you have these thoughts at any time, tell your doctor or go to a hospital straight away—see section 2 'Thoughts of suicide and worsening of your depression or anxiety disorder'.
- If you have taken too many tablets tell your doctor or go to a hospital straight away. Do this even if you feel well. This is because taking too much of this medicine can be dangerous.
- Do not stop taking your tablets or change the amount you take without checking with your doctor first. Keep taking them even if you feel better. If you stop taking Venlafaxine suddenly you may get withdrawal reactions—see section 3 'When and how to stop taking Venlafaxine tablets'.
- Taking some other medicines with Venlafaxine may cause problems. Tell your doctor if you are taking or have recently taken any other medicines—see section 2 'Taking Venlafaxine with other medicines'.
- Tell your doctor straight away if you feel restless and can't keep still, feel 'high' or over-excited or have jerky muscle movements which you can't control—see section 4 'Possible side effects'.
- If you have problems with your heart or have high blood pressure, talk to your doctor before taking Venlafaxine—see section 2 'Before you take Venlafaxine tablets'.
- If you are pregnant, planning to become pregnant, or are breast-feeding, talk to your doctor before taking Venlafaxine—see section 2 'Pregnancy and breast feeding'.

There is more information on all of these points in the rest of this leaflet.

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

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

1. WHAT VENLAFAXINE TABLETS ARE AND WHAT THEY ARE USED FOR
Venlafaxine Tablets contain Venlafaxine Hydrochloride as the active ingredient. Venlafaxine belongs to the class of medicines called "antidepressants" which are used to relieve the symptoms of depressive illness and any associated anxiety. People who are depressed may have lower levels than usual of substances called "serotonin" and "noradrenaline" in their brain. While it is not fully understood how anti-depressants work, Venlafaxine may help by increasing the levels of these substances in your brain.

Why Do You Need To Take These Tablets
You have been given Venlafaxine Tablets because you are suffering from the symptoms of depressive illness. Venlafaxine Tablets can relieve these symptoms and help you feel better.
Your doctor may continue to give you Venlafaxine tablets even when you are feeling better to prevent your symptoms from returning or prevent you from becoming depressed in the future.
If you need any further information on your condition, please ask your doctor.

REMEMBER: These tablets are for you. Only a doctor may prescribe them for you. Never give your tablets to other people. They may harm other people.

2. BEFORE YOU TAKE VENLAFAXINE TABLETS
Do not take Venlafaxine tablets if:
- You are allergic to any of the ingredients in Venlafaxine Hydrochloride Tablets.
- You are under 18 years old
- You are taking or have recently taken (within the last two weeks) another antidepressant drug known as a monoamine oxidase inhibitor's (MAOIs). These include phenelzine, isocarboxazid or selegiline. This is because taking these medicines together with Venlafaxine can cause serious or even life-threatening side effects. Also you must wait at least one week after you stop taking Venlafaxine tablets before you can take an MAOI.
- Do not take these tablets if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Venlafaxine.

You should tell your doctor or pharmacist if:
- You have liver or kidney disease.
UKPAR Venlafaxine 37.5 mg & 75 mg Tablets

- You have ever had heart problems or high blood pressure (ask your doctor if you are not sure).
- You have had epilepsy, seizures, fits or convulsions.
- You are taking cimetidine (a stomach drug) and are elderly or have liver problems, since cimetidine might increase the effect of Venlafaxine Tablets.
- You are suffering from, or have a history of, mania.
- You have ever had eye problems such as narrow angle glaucoma (increased pressure in the eye).
- You are taking warfarin (blood thinner), haloperidol or clozapine or other drugs for schizophrenia.
- You are taking medication for AIDS.
- You are breast feeding.
- You have bleeding problems such as bruising easily, bleeding from your gums or nosebleeds.

If you are not sure whether any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
- If you have previously had thoughts about killing or harming yourself
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.
- If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

Dry mouth

Dry mouth is reported in 1 in 10 patients treated with Venlafaxine. This may increase the risk of tooth decay (dental caries). Therefore, you should take special care with your dental hygiene.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

You may feel worse before you feel better

Venlafaxine may not work straight away. After you start treatment, you may feel worse before you feel better. It may take between two to four weeks before you start feeling better. Your doctor may ask to see you again in a couple of weeks and then regularly until you start feel well again. Tell your doctor if you do not start feeling better.

Use in children and adolescents under 18 years of age

Venlafaxine should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Venlafaxine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Venlafaxine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Venlafaxine. Also, the long-term safety concerning growth, maturation and development of the brain in this age group have not yet been demonstrated.

Taking Venlafaxine with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Venlafaxine can affect the way some other medicines work. Also, some other medicines can affect the way Venlafaxine works.

Do not take Venlafaxine and tell your doctor if you are taking or have recently taken:
- Medicines called “Monoamine Oxidase Inhibitors” or MAOIs. See section 2 - Do not take Venlafaxine tablets if.

Check with your doctor before taking Venlafaxine if you are taking any of the following medicines. They may want to check you regularly:
- Medicines for migraine such as sumatriptan (triptans)
- Medicines for depression such as SNRI, SSRIs, tricyclics, or medicines containing lithium
- Antibiotics, such as linezolid, used to treat infections
- Medicines used to treat depression such as modafinil (called reversible MAOIs)
- Medicines to help with weight loss such as sibutramine
- Painkillers containing Tramadol
- Herbal products such as St John’s Wort (also called Hypericum perforatum) or tryptophan supplements

Taking any of the above medicines with Venlafaxine can cause a potentially life-threatening condition called serotonin syndrome. Signs and symptoms of serotonin syndrome may include a combination of the following: restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, nausea, coma, vomiting. Get medical care straight away if you think this is happening to you. If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Venlafaxine.

The following medicines may also interact with Venlafaxine and should be used with caution. It is especially important to mention to your doctor or pharmacist if you are taking medicines containing:
**UKPAR Venlafaxine 37.5 mg & 75 mg Tablets**

- Ketoconazole (to treat fungal infections)
- Haloperidol or risperidone (to treat psychiatric conditions)
- Metoprolol (a beta blocker to treat high blood pressure and heart problems)

**Taking Venlafaxine Tablets with food and drink**
- Take Venlafaxine with food
- You should avoid alcohol while you are taking Venlafaxine Tablets.

**Pregnancy**
If you are pregnant or planning to get pregnant, talk to your doctor before taking Venlafaxine. It is not advisable to get pregnant while taking Venlafaxine so you should use contraception. Please ask your doctor if you have any questions about the right contraception for you.

If you become pregnant while taking Venlafaxine talk to your doctor straight away. Depending on how well Venlafaxine is working for you, they may decide it is better for you to:
- Gradually stop taking the medicine while you are pregnant
- Continue taking the medicine

If you are taking this medicine and you find out that you are pregnant, make sure your midwife and/or doctor know you are on Venlafaxine Tablets. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

**Breast-feeding**
Do not breast-feed if you are taking Venlafaxine. This is because small amounts may pass into the mother’s milk.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

**Effect on the ability to drive and use machines.**
Venlafaxine Tablets may make you feel tired, dizzy or affect your judgement. Make sure your judgement or coordination is not affected before you drive or use machinery. If you are not sure if any of the above applies to you, talk to your doctor or pharmacist.

**Important information about some of the ingredients of Venlafaxine Tablets**
This medicine contains Lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking these tablets.

**3. HOW TO TAKE VENLAFAXINE TABLETS**
Always take Venlafaxine tablets as advised by your doctor. The usual starting dose is one 37.5 mg tablet twice a day. You should take one tablet in the morning and one in the evening. However, your doctor may decide a different dose, up to a maximum of 375 mg a day, is better for you; do not take more than advised by your doctor.

The label on your medicine will tell you how many tablets to take and how often. If it does not, or you are not sure, ask your doctor or pharmacist.

**Children and adolescents under 18 years of age:**
Venlafaxine Tablets should not be used for children and adolescents under 18 years because it has not been proven to be an effective medicine in this age-group. In specific circumstances your doctor may have given you (or your child) this medicine for another reason and you want to discuss this, please go back to your doctor.
- Swallow the tablets whole with a drink of water. Do not crush, break or chew the tablet.
- Try to take the tablets at the same time each day.
- Do not take more tablets than your doctor tells you to.
- Do not stop taking your tablets except on your doctor’s advice.

It may take a few weeks or more before you feel your medicine is helping you feel better and you may need to take Venlafaxine Tablets for several months.

**If you take more Venlafaxine Tablets than you should**
If you take too many tablets you must seek immediate medical attention, even if you feel well, because of the risk of serious side effects. Remember to take the packet with you, even if it is empty.

The following effects may happen if you take too many tablets:
- A very fast heart beat
- Being drowsy, sleepy, confused or less aware of your surroundings than usual
- Blurred vision
- Fits (seizures)
- Being sick (vomiting)

**If you forget to take Venlafaxine Tablets**
If you miss a dose, try to take your next tablet as usual and continue your course. Do not take an extra tablet to make up.

**When and how to stop taking Venlafaxine Tablets**
Do not stop taking your tablets or change the dose without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Venlafaxine Tablets he/she will ask you to reduce your dose slowly before stopping treatment altogether. This should help reduce the chance of withdrawal symptoms.

If Venlafaxine Tablets are stopped suddenly or the dose is reduced too quickly, some patients may experience symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, dry mouth, loss of appetite, feeling or being sick, diarrhoea, nervousness, agitation, confusion, tinnitus (ringing in the ears), tingling or rarely electric shock sensations, weakness, poor co-ordination, tremor, sweating or seizures.

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

Like all medicines, Venlafaxine Tablets may cause unwanted effects in some people. Most side effects are mild and do not last for long. Serious side effects only occur rarely.

Stop taking Venlafaxine and see a doctor or go to a hospital straight away if:

- You have muscle weakness, tenderness or pain, feel unwell or have a high temperature, or feel sick, 
- You may have a rare but serious illness that can be life-threatening, called ‘rhabdomyolysis’ 
- You get swelling of your hands, feet, ankles, face, lips or throat which may cause difficulty in swallowing or breathing. You could also notice an itchy, lumpy rash (hives) or nettle rash (urticaria). You may be having an allergic reaction to Venlafaxine 
- You get blistering or peeling of skin around your lips, eyes, mouth, nose and genitals, with flu-like symptoms and fever. These could be signs of an illness called “Stevens-Johnson syndrome” 
- You have a very high temperature, sweating, stiff muscles, fast heart rate, fast breathing and drowsiness or confusion. You may also have difficulty in walking; have twitching or jerking movements you cannot control. These could be signs of a serious condition called neuroleptic malignant syndrome.

Tell your doctor straight away if:

- You notice yellowing of your skin or eyes and your urine becomes darker in colour. You may also have a high temperature, feel tired, lose your appetite, have stomach pain or feel sick. These could be signs of a liver problem, such as jaundice or hepatitis 
- You feel agitated, confused, sweat more than usual, have diarrhoea, a high temperature, higher blood pressure than usual, sudden jerking of your muscles and an unusually fast heart beat. These could be signs of an illness called “serotonin syndrome” 
- You can get severe stomach pain which may reach through to your back. This could be a sign of pancreatitis, 
- You feel unwell, lose your appetite, have a fever lasting 2 to 3 days, and have difficulty breathing, shortness of breath and a cough. This could be due to a lung problem (pulmonary eosinophilia). You notice blood in your vomit or pass black tarry stools. These may be signs of bleeding in your stomach or bowel 
- You have fits (seizures) or, in patients with epilepsy, you notice an increase in the number of seizures 
- You feel high or over-excited, see or hear things which are not there (hallucinations) and have difficulty concentrating or staying still (mania, hypomania or delirium) 
- You feel unwell, confused, irritable or weak. You may also lose your appetite. This could be an illness called syndrome of inappropriate anti-diuretic hormone secretion (SIADH) 
- You have painful eyes with blurred vision. These could be the signs of glaucoma (increased pressure in the eye) 

The side effects above are either rare (affect less than 1 in 1,000 people) or very rare (affect less than 1 in 10,000 people).

An increased risk of bone fractures has been observed in patients taking this type of medicines.

If any of the following side effects gets serious or lasts longer than a few days, tell your doctor or pharmacist.

- Feeling sick, constipation
- Headache, unusual tiredness or weakness, sweating, dizziness, dry mouth, difficulty in sleeping or drowsiness, nervousness

Very common (Likely to affect more than 1 in 10 people):
- Loss of appetite (anorexia), constipation being sick (vomiting) 
- Chills, fever and heart problems including high blood pressure, palpitations, flushing 
- Agitation, confusion, abnormal dreams 
- Sore muscles or painful joints, tremor 
- Skin rash, strange feeling on the skin such as “pins and needles” or burning 
- Passing urine more or less than usual 
- Reduced sex drive, impotence and menstrual disturbances in women such as increased bleeding or irregular bleeding 
- Blurred vision, tinnitus (ringing in the ears) 
- Difficulty in breathing (dyspnoea) or yawning 
- Being drowsy, finding it difficult to sleep or having strange dreams 
- Feeling separated or detached from reality

Common (Likely to affect less than 1 in 10 people):
- Loss of appetite (anorexia), constipation being sick (vomiting) 
- Chills, fever and heart problems including high blood pressure, palpitations, flushing 
- Agitation, confusion, abnormal dreams 
- Sore muscles or painful joints, tremor 
- Skin rash, strange feeling on the skin such as “pins and needles” or burning 
- Passing urine more or less than usual 
- Reduced sex drive, impotence and menstrual disturbances in women such as increased bleeding or irregular bleeding 
- Blurred vision, tinnitus (ringing in the ears) 
- Difficulty in breathing (dyspnoea) or yawning 
- Being drowsy, finding it difficult to sleep or having strange dreams 
- Feeling separated or detached from reality

Uncommon (Likely to affect less than 1 in 100 people):
- Feeling dizzy or unsteady on standing due to a fall in blood pressure (especially for elderly patients) 
- Heart problems including an abnormal heartbeat, faster or slower than usual heart rate, flushing or fainting 
- Clenching or grinding of teeth, muscle spasm 
- Lack of emotion or interest in things (apathy), seeing or hearing things which are not there (hallucinations) 
- Difficulty in urinating 
- Increased sensitivity of your skin to sunlight 
- Altered taste sensation 
- Weight gain 
- Diarrhoea 
- Skin rash 
- Tinnitus (ringing in your ears) 
- Wide spread bruising 
- Loss of balance and co-ordination 
- Abnormal hair loss
Rare (Likely to affect less than 1 in 1000 people):
- Feeling aggressive or having aggressive thoughts - this is more likely at the start of, and after stopping, treatment
- Itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis)
- Stiff muscles, rarely clumsiness or loss of balance, slurring or difficulty in speaking
- Severe skin rash which may lead to blistering and peeling of the skin
- Erythema multiforme, Stevens Johnson syndrome (these are both rare but serious skin conditions)
- Black tarry stools (faeces) which can be a sign of internal bleeding

Very rare (Likely to affect less than 1 in 10,000 people):
- Feeling of restlessness or unable to sit or stand still
- Disorientation and confusion often accompanied by hallucination (delirium)
- Serious chest pain and collapse

Frequency unknown (cannot be estimated from available data)
- Abnormal production of breast milk (in both men and women)
- Bruising more easily than usual, bleeding more or for longer than usual after an injury, unusual bleeding from gums, or elsewhere, a rash of purple dark red spots under the skin, getting infections more easily than usual, These could be the signs of blood problem. Tell your doctor if this happens to you.
- Thoughts of harming or killing yourself

Blood tests
The following side effects also affect blood. They are only found in blood test results:
- Increase in blood cholesterol levels
- Changes to some of the cells or other parts of your blood
- Changes in the way your liver is working
- Changes in the levels of sodium in your blood
- Reduced platelet count in your blood which leads to increased risk of bruising and bleeding.

Your doctor may wish to do blood tests occasionally, particularly if you have been taking Venlafaxine for a long time.
You should also tell your doctor if you notice any other unwanted effect not mentioned above.

5. HOW TO STORE VENLAFAXINE TABLETS
- Keep out of the reach and sight of children.
- Do not store above 25°C. Store in the original package.
- Do not put the tablets into another container, they might get mixed up. Do not remove the tablets from the blister pack or open the blister pack until you are ready to take the medicine.
- Do not use these Tablets after the “Expiry Date” which is stated on the carton or blister. The expiry date refers to the last day of that month.

Remember: This medicine is for you. Do not share it with anyone else. It may not suit them.
Medicines should not be disposed of via waste water of household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Always return any left-over medicine to your pharmacist. Only keep it if your doctor tells you to.

6. FURTHER INFORMATION

What Venlafaxine Tablets contain
Each tablet contains Venlafaxine Hydrochloride Ph.Eur equivalent to Venlafaxine 37.5 mg and 75 mg as the active ingredient.
As well as Venlafaxine Hydrochloride, the tablet contains lactose, microcrystalline cellulose, sodium starch glycolate, pregelatinised starch, magnesium stearate, yellow iron oxide (E172) and red iron oxide (E172).

What Venlafaxine Tablets look like and contents of the pack
Venlafaxine Tablets 75 mg are Peach colour, circular, flat bevelled edged uncoated tablets having embossed ‘75’ on one side and ‘BL’ on other side.
Venlafaxine Tablets 37.5 mg are Peach colour, circular, flat bevelled edged uncoated tablets having embossed ‘37.5’ on one side and ‘BL’ on other side.
Venlafaxine Tablets 75 mg and 37.5 mg are packed in blister pack of 28 and 56 tablets.

Marketing Authorisation Holder and Manufacturer
Bristol Laboratories Ltd,
Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EG, UK
Venlafaxine 37.5 mg Tablets: PL 17907/0250
Venlafaxine 75 mg Tablets: PL 17907/0251
This leaflet was last approved: April 2011
Version 003
UKPAR Venlafaxine 37.5 mg & 75 mg Tablets

PL 17907/0250-1

LABELLING

Venlafaxine 37.5 mg Tablets - PL 17907/0250

Carton for blisters, with Braille – pack size 28
Carton for blisters, with Braille – pack size 56
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Venlafaxine 37.5 mg Tablets

Blister foil
Venlafaxine 75 mg Tablets - PL 17907/0251

Carton for blisters, with Braille – pack size 28
Carton for blisters, with Braille – pack size 56
Venlafaxine
75 mg
Tablets

Blister foil