Venlafaxine 25 mg Tablets

PL 08608/0074, 0078 and 0082

Venlafaxine 50 mg Tablets

PL 08608/0076, 0080 and 0084

(venlafaxine hydrochloride)

UK Public Assessment Report

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Medicines and Healthcare Products Regulatory Agency

VENLAFAXINE 25MG TABLETS

PL 08608/0074, 0078 and 0082

VENLAFAXINE 50MG TABLETS

PL 08608/0076, 0080 and 0084

(venlafaxine hydrochloride)

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Olinka UK Limited Marketing Authorisations (licences) for the medicinal products Venlafaxine 25mg Tablets (PL 08608/0074, 0078 and 0082) and Venlafaxine 50mg Tablets (PL 08608/0076, 0080 and 0084) on 17 September 2008. These are prescription-only medicines (POM) used for the treatment of depression and to prevent relapses or recurrence of depression. Venlafaxine tablets are also used to treat anxiety.

Venlafaxine tablets contain the active ingredient venlafaxine, as venlafaxine hydrochloride, which is an anti-depressant.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Venlafaxine 25mg and 50mg Tablets outweigh the risk; hence Marketing Authorisations have been granted.

The Marketing Authorisations subsequently underwent Change of Ownership procedures; the subsequent Marketing Authorisations were all eventually cancelled.

VENLAFAXINE 25MG TABLETS

PL 08608/0074, 0078 and 0082

VENLAFAXINE 50MG TABLETS

PL 08608/0076, 0080 and 0084

(venlafaxine hydrochloride)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Olinka UK Limited Marketing Authorisations for the medicinal products Venlafaxine 25mg Tablets (PL 08608/0074, 0078 and 0082) and Venlafaxine 50mg Tablets (PL 08608/0076, 0080 and 0084) on 17 September 2008. These are prescription-only medicines (POM).

These national, abridged applications are for two strengths of immediate-release film-coated tablets containing 25mg and 50mg of the serotonin and noradrenaline re-uptake inhibitor (SNRI) venlafaxine. The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal versions of the UK reference products, Efexor 25mg and 50mg Tablets (PL 00011/0198 and 0200) respectively, authorised to John Wyeth and Brother Limited on 27 November 1994. The innovator products, Efexor 25mg and 50mg Tablets, granted to Wyeth Pharmaceuticals BV (Netherlands) in June 1994, have been authorised in the EU for more than 10 years, so the period of data exclusivity has expired.

The active ingredient, venlafaxine hydrochloride, belongs to the pharmacotherapeutic group of drugs called 'other antidepressants'. Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. These products are indicated for the treatment of depressive illness including depression accompanied by anxiety. 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 applications for Venlafaxine 25mg and 50mg Tablets all depend on the single bioequivalence study presented comparing the applicant's 37.5mg product with the UK reference product Efexor 37.5mg Tablets. Consequently, all sections of the Scientific Discussion refer to both strengths of the products. As the test products, Venlafaxine 25mg and 50mg Tablets, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 37.5mg strength were extrapolated to the other tablet strengths.

The Marketing Authorisations subsequently underwent Change of Ownership procedures; the subsequent Marketing Authorisations were all eventually cancelled.

PHARMACEUTICAL ASSESSMENT

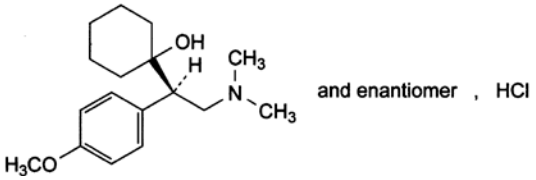
ACTIVE SUBSTANCE

Venlafaxine hydrochloride

Nomenclature:

INN:	Venlafaxine
Chemical names:	i) (±)-1-[2-(Dimethylamino)-1-(4-methoxy phenyl)ethyl]cyclohexanol hydrochloride
	ii) N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine hydrochloride

Structure:



Molecular formula:	$C_{17}H_{27}NO_2.HCl$
Molecular weight:	313.9
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.
Stereochemistry:	It displays polymorphism. It is a racemate with two active enantiomers.

The active substance, venlafaxine hydrochloride, is the subject of a European Pharmacopoeia (EP) monograph.

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. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal or biological origin, and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed into double polythene bags as the primary container. The polythene bags are then packed into triple laminated high barrier bags. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years.

DRUG PRODUCT

Description and Composition

The drug products are presented as orange, round, biconvex, film-coated tablets containing 25mg and 50mg of venlafaxine base (see SmPCs / patient information leaflet for full descriptions of tablets).

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, povidone K30, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate making up the tablet core; and titanium dioxide (E171), hypromellose 6 cP, macrogol 400, and sunset yellow FCF lake (E110) constituting 'Opadry 03B23319 Orange' which makes up the tablet coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Opadry 03B23319 Orange which makes up the tablet coating, and one of its constituents, sunset yellow FCF lake (E110). These both comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate 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.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity data for each strength were provided for the generic tablets and appropriate comparator products (including originator products) sourced from various markets. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are 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 product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished products are marketed in PVC (polyvinylchloride) / aluminium blister strips, or in HDPE containers with LDPE (low density polyethylene) screw caps; either of which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in pack sizes of 14, 28, 30, 42 and 56 film-coated tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 48 months has been set, which is satisfactory. There are no special precautions for storage.

Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Venlafaxine 37.5mg tablets, to the reference product, Efexor 37.5mg tablets (Wyeth Laboratories, UK).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Venlafaxine 37.5mg tablets is a generic medicinal product of Efexor 37.5mg tablets appears justified. As the test products, Venlafaxine 25mg, 37.5mg and 50mg tablets, meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 37.5mg strength were extrapolated to the 25mg and 50mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was, therefore, recommended that Marketing Authorisations be granted.

PRECLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Venlafaxine 25mgand 50mg Tablets, products claiming to be generic medicinal versions of Efexor 25mg and 50mg Tablets (John Wyeth and Brother Limited) respectively.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified expert and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Venlafaxine 25mg and 50mg tablets are indicated for the treatment of depressive illness including depression accompanied by anxiety. 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.

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

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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.

No new data 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 serotonin and noradrenaline re-uptake inhibitors (SNRI) 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.

Pharmacokinetics

No new data 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. O-desmethylvenlafaxine (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.

Pharmacokinetics - Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Venlafaxine 37.5mg tablets, to the reference product, Efexor 37.5mg tablets (Wyeth Laboratories, UK). Satisfactory Certificates of Analysis for the test and reference products were provided. The study was conducted in accordance with current standards of Good Clinical Practice.

The design was a randomised, open, two-treatment, two-period, two-way crossover, single dose bioequivalence study, performed in 40 healthy adult human volunteers (plus two alternates) under fasting conditions. Single oral 37.5mg doses were separated by an adequate washout period of 14 days. Serum drug levels were followed for 48 hours following dosing. An adequate statistical plan was provided. Both Log-transformed and non-transformed data for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, and C_{max} were analysed by ANOVA.

Bio-study outcome and results:

Of the 42 (40 + 2 alternates) enrolled, only 29 evaluable subjects completed the clinical part of the study, due mainly to the occurrence of nausea and vomiting. Therefore it was decided to dose 11 additional subjects with 5 further alternates in order to reach the originally planned sample size of 40. 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 below:

Pharmacokinetic results (mean + (SD)) for a randomised single dose 2-way crossover study between the test and reference products. Log transformed. ANOVA. n=40 healthy subjects, dosed fasted; t=48 hours. Wash-out period: 2 weeks

Test parameter	**Test product** (geometric means)	**Reference product** (geometric means)	**Ratio (%) Test/reference x 100**	**90% Confidence intervals (%)**
Venlafaxine				
$AUC_{0\text{-}t}$ (ng.h/ml)	491.39 (479.86)	472.67 (482.03)	103.8	98.4 -109.5
$AUC_{0\text{-}\infty}$ (ng.h/ml)	509.62 (520.77)	491.94 (532.73)	103.8	98.5 – 109.4
C_{max} (ng/ml)	61.18 (30.89)	57.58 (25.83)	104.3	98.1 – 111.0
T_{max} (h)*	1.87 (0.83)	1.74 (0.83)	-	-
$T_{½}$	5.11 (2.48)	5.29 (2.66)	-	-
O-desmethylvenlafaxine				
$AUC_{0\text{-}t}$ (ng.h/ml)	1499.1 (370.31)	1513.2 (391.19)	99.2	95.9 – 102.6
$AUC_{0\text{-}\infty}$ (ng.h/ml)	1573.5 (394.26)	1586.3 (417.93)	99.4	96.1 – 102.8
C_{max} (ng/ml)	87.23 (26.34)	87.55 (26.86)	99.5	96.7 – 102.4
T_{max} (h)*	3.93 (1.87)	3.57 (1.92)	-	-
$T_{½}$	10.24 (2.71)	10.16 (2.43)	-	-

* median values - non-parametric confidence intervals (*Hauschke et al.*)

The 90% confidence intervals for the log-transformed parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0 – 125.0%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions.

As these applications for bothstrengths are supported by a single bio-study 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 tablets or oral solution. Given that the three strengths are based on a proportional formulation, that similar dissolution profiles occur for the threestrengths and that it has been established

that kinetics of venlafaxine and the active metabolite are linear up to 450mg, it is acceptable that a bioequivalence study has not been performed on the 25 and 50 tablets.

Overall conclusions on pharmacokinetics

The 90% confidence intervals for the test/reference lie within the accepted 80-125% bioequivalence range for both venlafaxine and its major metabolite (O-desmethylvenlafaxine). Bioequivalence of the test product to the reference formulation has, therefore, been satisfactorily demonstrated in accordance with CHMP criteria.

The multiple dose waiver criteria are met and hence the single study on the 37.5mg strength is accepted as demonstrating bioequivalence for the other product strengths.

EFFICACY

Efficacy is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

No new data are submitted and none are required for these types of application.

SAFETY

Safety is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

No new data are submitted and none are required for these types of application.

EXPERT REPORT

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

PRODUCT INFORMATION:

Summary of Product Characteristics

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

Patient Information Leaflet

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 37.5mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 25mg and 50mg strength tablets.

Sufficient clinical information has been submitted to support these applications. When used as indicated, venlafaxine has a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Venlafaxine 25mg and 50mg 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 the reference product Efexor 37.5mg tablets (Wyeth Laboratories, UK). As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), and the pharmacokinetics of venlafaxine are linear over the proposed dose range, the results and conclusions of the bioequivalence study on the 37.5mg strength were extrapolated to the 25mg and50mg strengths. Thus, no separate bioequivalence studies were necessary for these strengths.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for Efexor 25mg and 50mg tablets.

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

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. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

VENLAFAXINE 25MG TABLETS

PL 08608/0074, 0078 and 0082

VENLAFAXINE 50MG TABLETS

PL 08608/0076, 0080 and 0084

(venlafaxine hydrochloride)

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 14 December 2004.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 05 October 2005.

3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 07 December 2005, and subsequently 05 December 2007.

4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 22 March 2006 and 13 March 2008 respectively.

5 Upon review of responses, the MHRA requested further information relating to the quality sections on 04 April 2008 and further information relating to the clinical sections on 14 April 2008.

6 The applicant responded to the MHRA's request, providing further information for the quality and clinical sections on 07 May 2008.

7 The applications were determined on 17 September 2008.

VENLAFAXINE 25MG TABLETS

PL 08608/0074, 0078 and 0082

VENLAFAXINE 50MG TABLETS

PL 08608/0076, 0080 and 0084
(venlafaxine hydrochloride)

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Venlafaxine 25 mg Tablets (PL 08608/0074, 0078 & 0082) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Venlafaxine 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Venlafaxine 25 mg Tablet contains 25 mg venlafaxine as venlafaxine hydrochloride

Excipients: Lactose monohydrate and Sunset Yellow (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets

Orange, 6 mm round biconvex, film-coated tablets. Marked V1

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Venlafaxine is indicated for the treatment of depressive illness including depression accompanied by anxiety.

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 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine tablets are taken with food. If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.

In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed and 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 minimal effective dose, consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).

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

Patients with Renal or Hepatic Impairment:

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

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

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

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 Contra-indications and 4.8 Undesirable Effects).*

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.

Discontinuing Venlafaxine:

Discontinuation effects are well known to occur with the abrupt withdrawal of other antidepressants *(see 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to venlafaxine or to any of the excipients.
- Concomitant use of venlafaxine with monoamine oxidase inhibitors *(See Interactions with other Medicinal Products and Other Forms of Interactions).*
- Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder *(see section 4.4 Special warnings and Precautions for* Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- *Suicide/suicidal thoughts or clinical worsening:* depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement nay 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.
- Activation of manic of 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.
- Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

Clinically significant electrocardiogram findings were observed in 1% of venlafaxine-treated patients compared with 0.2% of placebo-treated patients. Clinically significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

- Venlafaxine should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure.
- Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. The presence of treated hypertension or elevated blood pressure at baseline did not seem to predispose patients to further increases during venlafaxine therapy.
- 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.
- 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.
- Dosage should be reduced in patients with moderate to severe renal impairment or hepatic cirrhosis *(see sections 4.2 and 4.5).*
- Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.
- 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.
- 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.
- There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptakeinhibitors (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.
- 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.
- 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.
- 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.
- Use in children and adolescents under 18 years of age. Venlafaxine Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- The colouring sunset yellow FCF (E110) may cause allergic reactions.

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, andhyperthermia 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 Contra-indications).*

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).

Lithium:

Venlafaxine had no effect on the pharmacokinetics of lithium.

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_{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_{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:

Venlafaxine is primarily metabolised to its equally active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. However, unlike many other antidepressants, no dosage adjustment is necessary when Venlafaxine is administered concomitantly with drugs which inhibit CYP2D6, or when used in patients who are poor CYP2D6 metabolisers, since the total concentration of active compound (venlafaxine and ODV) is not affected.

The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Therefore, caution should be used with concomitant intake of drugs which inhibit both of these enzymes. Such interactions have not been studied to date.

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 C_{max} 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 Special Warnings and Precautions for Use.

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

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

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

Blood and lymphatic system disorders

Uncommon: ecchymosis, mucous membrane bleeding;

Rare: prolonged bleeding time, haemorrhage, thrombocytopenia;

Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (*see Special Warnings and Precautions for Use*)

Common: hypertension, palpitation, vasodilatation;

Uncommon: 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, diarrhoea, dyspepsia, vomiting;

Uncommon: bruxism;

Rare: gastrointestinal bleeding;

Very rare: pancreatitis.

General disorders

Very common: asthenia, headache;

Common: abdominal pain, chills, pyrexia;

Rare: anaphylaxis

Metabolic and nutritional disorders

Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see *Special Warnings and Precautions for Use),*weight gain or loss;

Uncommon: hyponatraemia including SIADH *(see Special Warnings and Precautions for Use),* 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: hallucinations, myoclonus;

Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, extrapyramidal disorders including dyskinesia, dystonia, mania or hypomania *(see Special Warnings and Precautions for Use),* neuroleptic malignant syndrome-like effects, seizures *(see Special Warnings and Precautions for Use),* serotonergic syndrome;

*Very rare:*delirium.

Renal and urinary disorders

Common: urinary frequency;

Uncommon: urinary retention.

Reproductive and breast disorders

Very common: abnormal ejaculation/orgasm;

Common: decreased libido, impotence, menstrual cycle disorders;

Rare: galactorrhoea.

Respiratory system disorders

Common: dyspnoea, yawning;

Very rare: pulmonary eosinophilia.

Skin and subcutaneous tissue disorders

Very common: sweating (including night sweats);

Common: pruritus, rash;

Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia;

Rare: 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.

Special Notes:

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

Withdrawal reactions reported on abrupt cessation, dose reduction or tapering of venlafaxine include fatigue, somnolence, headache, nausea or vomiting, loss of appetite, dizziness, light-headedness, anorexia, dry mouth,diarrhoea, insomnia, nightmares, nervousness, agitation, anxiety,confusion, hypomania, weakness, decreased co-ordination, tinnitus, tremor, convulsions, paraesthesia, sweating and vertigo. The majority of symptoms experienced on withdrawal of Venlafaxine are non-serious and self-limiting (see also Posology and Administration).

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

4.9 OVERDOSE

Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia and seizures, hypotension 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

There have been reports of fatalities in patients taking overdoses of Venlafaxine, predominantly 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX16

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

The mechanism of Venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

5.2 PHARMACOKINETIC PROPERTIES

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

5.3 PRECLINICAL SAFETY DATA

None

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Magnesium stearate

Tablet Coating:

Opadry 03B23319 Orange containing;

Hypromellose 6 cP
Titanium dioxide (E171)
Macrogol / PEG 400
Sunset yellow FCF lake (E110)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

48 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

No special precautions for storage

6.5 NATURE AND CONTENTS OF CONTAINER

Al/PVC Blister

HDPE Container with LDPE screw Cap

14, 28, 30, 42, 56 tablets

* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited

38/40 Chamberlayne Road

London

NW10 3JN

8 MARKETING AUTHORISATION NUMBER(S)

PL 08608/0074, 0078 & 0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/09/2008

10 DATE OF REVISION OF THE TEXT

17/09/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Venlafaxine 50 mg Tablets (PL 08608/0076, 0080 & 0084) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Venlafaxine 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Venlafaxine 50 mg Tablet contains 50 mg venlafaxine as venlafaxine hydrochloride

Excipients: Lactose monohydrate and Sunset Yellow (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets

Orange, 8 mm round biconvex, film-coated tablets. Marked V3

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Venlafaxine is indicated for the treatment of depressive illness including depression accompanied by anxiety.

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 75mg per day given in two divided doses (37.5mg twice daily). Most patients respond to this dose. It is recommended that venlafaxine tablets are taken with food. If, after an adequate trial and evaluation, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily). There may be an increased risk of side effects at higher doses and dose increments should be made only after a clinical evaluation and after at least 3-4 weeks of therapy (see section 4.4). The lowest effective dose should be maintained.

In more severely depressed or hospitalised patients, and under close supervision of a physician, the daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. In those more severely depressed and 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 minimal effective dose, consistent with patient response and tolerance. A limited amount of venlafaxine should be provided to reduce the risk from overdose (see section 4.4).

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

Patients with Renal or Hepatic Impairment:

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

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

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

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 Contra-indications and 4.8 Undesirable Effects).*

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.

Discontinuing Venlafaxine:

Discontinuation effects are well known to occur with the abrupt withdrawal of other antidepressants *(see 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to venlafaxine or to any of the excipients.
- Concomitant use of venlafaxine with monoamine oxidase inhibitors *(See Interactions with other Medicinal Products and Other Forms of Interactions).*
- Venlafaxine should not be used in children and adolescents under the age of 18 years with Major Depressive Disorder *(see section 4.4 Special warnings and Precautions for* Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- *Suicide/suicidal thoughts or clinical worsening:* depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement nay 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.
- Activation of manic of 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.
- Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

Clinically significant electrocardiogram findings were observed in 1% of venlafaxine-treated patients compared with 0.2% of placebo-treated patients. Clinically significant changes in PR, QRS or QTc intervals were rarely observed in patients treated with venlafaxine during clinical trials.

- Venlafaxine should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure.
- Dose-related increases in blood pressure have been reported particularly in patients receiving daily doses greater than 200mg. Measurement of blood pressure is therefore recommended for patients receiving venlafaxine. The presence of treated hypertension or elevated blood pressure at baseline did not seem to predispose patients to further increases during venlafaxine therapy.
- 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.
- 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.
- Dosage should be reduced in patients with moderate to severe renal impairment or hepatic cirrhosis *(see sections 4.2 and 4.5).*
- Postural hypotension has been observed occasionally during venlafaxine treatment. Patients, especially the elderly, should be alerted to the possibility of dizziness or unsteadiness.
- 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.
- 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.
- There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with serotonin-reuptakeinhibitors (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.
- 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.
- 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.
- 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.
- Use in children and adolescents under 18 years of age. Venlafaxine Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- The colouring sunset yellow FCF (E110) may cause allergic reactions.

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, andhyperthermia 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 Contra-indications).*

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).

Lithium:

Venlafaxine had no effect on the pharmacokinetics of lithium.

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_{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_{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:

Venlafaxine is primarily metabolised to its equally active metabolite, ODV, by the cytochrome P450 enzyme CYP2D6. However, unlike many other antidepressants, no dosage adjustment is necessary when Venlafaxine is administered concomitantly with drugs which inhibit CYP2D6, or when used in patients who are poor CYP2D6 metabolisers, since the total concentration of active compound (venlafaxine and ODV) is not affected.

The major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Therefore, caution should be used with concomitant intake of drugs which inhibit both of these enzymes. Such interactions have not been studied to date.

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 C_{max} 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 Special Warnings and Precautions for Use.

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

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

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

Blood and lymphatic system disorders

Uncommon: ecchymosis, mucous membrane bleeding;

Rare: prolonged bleeding time, haemorrhage, thrombocytopenia;

Very rare: blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia and pancytopenia).

Cardiovascular and vascular disorders (*see Special Warnings and Precautions for Use*)

Common: hypertension, palpitation, vasodilatation;

Uncommon: 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, diarrhoea, dyspepsia, vomiting;

Uncommon: bruxism;

Rare: gastrointestinal bleeding;

Very rare: pancreatitis.

General disorders

Very common: asthenia, headache;

Common: abdominal pain, chills, pyrexia;

Rare: anaphylaxis

Metabolic and nutritional disorders

Common: serum cholesterol increased (particularly with prolonged administration and possibly with higher doses (see *Special Warnings and Precautions for Use),* weight gain or loss;

Uncommon: hyponatraemia including SIADH *(see Special Warnings and Precautions for Use),* 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: hallucinations, myoclonus;

Rare: ataxia and disorders of balance and co-ordination, speech disorders including dysarthria, extrapyramidal disorders including dyskinesia, dystonia, mania or hypomania *(see Special Warnings and Precautions for Use),* neuroleptic malignant syndrome-like effects, seizures *(see Special Warnings and Precautions for Use),* serotonergic syndrome;

*Very rare:*delirium.

Renal and urinary disorders

Common: urinary frequency;

Uncommon: urinary retention.

Reproductive and breast disorders

Very common: abnormal ejaculation/orgasm;

Common: decreased libido, impotence, menstrual cycle disorders;

Rare: galactorrhoea.

Respiratory system disorders

Common: dyspnoea, yawning;

Very rare: pulmonary eosinophilia.

Skin and subcutaneous tissue disorders

Very common: sweating (including night sweats);

Common: pruritus, rash;

Uncommon: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions, alopecia;

Rare: 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.

Special Notes:

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

Withdrawal reactions reported on abrupt cessation, dose reduction or tapering of venlafaxine include fatigue, somnolence, headache, nausea or vomiting, loss of appetite, dizziness, light-headedness, anorexia, dry mouth,diarrhoea, insomnia, nightmares, nervousness, agitation, anxiety,confusion, hypomania, weakness, decreased co-ordination, tinnitus, tremor, convulsions, paraesthesia, sweating and vertigo. The majority of symptoms experienced on withdrawal of Venlafaxine are non-serious and self-limiting (see also Posology and Administration).

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

4.9 OVERDOSE

Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia and seizures, hypotension 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

There have been reports of fatalities in patients taking overdoses of Venlafaxine, predominantly 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX16

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

The mechanism of Venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine, are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine reuptake. In addition, venlafaxine and O-desmethylvenlafaxine reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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

5.2 PHARMACOKINETIC PROPERTIES

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

5.3 PRECLINICAL SAFETY DATA

None

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Magnesium stearate

Tablet Coating:

Opadry 03B23319 Orange containing;

Hypromellose 6 cP
Titanium dioxide (E171)
Macrogol / PEG 400
Sunset yellow FCF lake (E110)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

48 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

No special precautions for storage

6.5 NATURE AND CONTENTS OF CONTAINER

Al/PVC Blister

HDPE Container with LDPE screw Cap

14, 28, 30, 42, 56 tablets

* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited

38/40 Chamberlayne Road

London

NW10 3JN

8 MARKETING AUTHORISATION NUMBER(S)

PL 08608/0076, 0080 & 0084

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/09/2008

10 DATE OF REVISION OF THE TEXT

17/09/2008

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Venlafaxine 25mg, 37.5mg, 50mg and 75mg tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- If you have further questions, please ask your doctor or your 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.

In this leaflet:

1. WHAT VENLAFAXINE TABLETS ARE AND WHAT THEY ARE USED FOR

Venlafaxine tablets are an antidepressant and are used to treat depression and to prevent relapses or recurrence of depression.
Venlafaxine tablets are also used to treat anxiety.

2. BEFORE YOU TAKE VENLAFAXINE TABLETS

Do not take Venlafaxine tablets:
- if you are allergic (hypersensitive) to venlafaxine or any of the other ingredients of Venlafaxine tablets (see section 6). An allergic reaction may include rash, difficulty breathing or swelling of the face, throat or tongue.
- if you are taking or have recently taken, within the last two weeks, a different type of antidepressant medicine called a monoamine oxidase inhibitor (MAOI).

Venlafaxine tablets are not intended for children and adolescents under the age of 18 years.

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 effects concerning growth, maturation and development of the brain in this age group have not yet been demonstrated.
Taking other medicines:
Venlafaxine tablets are not to be used in combination with a monoamine oxidase inhibitor (MAOI) (a different type of antidepressant) or within two weeks of taking an MAOI. Taking a MAOI together with many medicines, including Venlafaxine tablets, may cause serious or even life-threatening adverse effects. You must wait at least 14 days after you have stopped taking an MAOI until you can take Venlafaxine tablets. Also, you need to wait at least one week after you stop taking Venlafaxine tablets before you can take an MAOI.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is important as using more than one medicine at the same time can strengthen or weaken the effect of the medicines. Your doctor may need to take special care or change the dose. This is especially important if you are using or have recently been using medicines like MAO inhibitors (see above), lithium or other antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), warfarin (blood thinner), medication for AIDS (e.g. indinavir), haloperidol, clozapine or other drugs for schizophrenia, cimetidine (a stomach drug), triptans e.g. sumatriptan and zolmitriptan (drugs for migraine) or medication to help you lose weight.

Take special care with Venlafaxine tablets:
Before taking Venlafaxine tablets, tell your doctor if you have any of these medical conditions:

- if you suffer from, or have suffered from mania (feeling high or over-excited).
- if you have had seizures (fits)
- if you have had a heart attack or have any other diseases of the heart
- if you have a history of drug dependence or abuse
- if you have liver or kidney disease
- if you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- if you have a rapid heart beat
- if you have a history of bleeding disorders (tendency to develop bruising)
- if you are taking neuroleptic medicines (such as haloperidol, clozapine or olanzapine)
- if you are taking medication to help you lose weight (such as phenetermine)
- if you are having electroconvulsive therapy (ECT) for depression.

The medicine may cause a rise in blood pressure, which for some patients may require close supervision by the doctor.

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.

- if you have previously had thoughts about killing and harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed 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.

Taking Venlafaxine tablets with food and drink:
Venlafaxine tablets should be taken with food.
You are advised to avoid alcohol consumption while taking Venlafaxine tablets.

Pregnancy and breastfeeding:
Tell your doctor if you become pregnant, or if you are trying to become pregnant, while you are taking Venlafaxine tablets. You should use Venlafaxine tablets only after discussing the potential benefits and any potential risks to your unborn child with your doctor.
The use of Venlafaxine tablets is not recommended whilst breast-feeding. You should ask your doctor for advice if you are breast-feeding.

Important information about some of the ingredients of Venlafaxine tablets:
Venlafaxine tablets contains lactose, if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. Also contains sunset yellow which may cause allergic reactions.

3. HOW TO TAKE VENLAFAXINE TABLETS

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

The usual starting dose is one 37.5mg 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 375mg a day, is better for you. The label 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.

Swallow the tablets whole with a drink of water. Do not crush or chew. It is recommended to take the tablets with food at approximately the same time every day.

It is quite normal that it may take a few weeks or more before you feel that your medicine is having an effect.

If you take more Venlafaxine tablets than you should:
If you take more than the amount of Venlafaxine tablets prescribed by your doctor, or if you think a child has swallowed any of the tablets, contact your doctor or your nearest hospital immediately. Overdose may cause dizziness, seizures

(fits), change in heart rhythm, decreased blood pressure and changes in level of consciousness. Take the leaflet, any remaining tablets and the container with you to the hospital or doctor so they know which tablets were taken.

If you forget to take Venlafaxine tablets:
If you forget to take a tablet, take one as soon as you remember, unless it is less than 12 hours until your next tablet is due, then wait and take the next dose at the unusual time. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Venlafaxine tablets:
Do not suddenly stop taking Venlafaxine without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Venlafaxine he/she will ask you to reduce your dose before stopping treatment altogether. If Venlafaxine is stopped suddenly or the dose reduced too quickly, some patients may experience withdrawal symptoms such as tiredness, dizziness, light-headedness, headache, sleeplessness, nightmares, agitation, anxiety, dry mouth, loss of appetite, feeling or being sick, diarrhoea, nervousness, confusion, tinnitus (ringing in the ears) 'pins and needles', vertigo, weakness, poor co-ordination, tremor, sweating or seizures. These symptoms are generally non-serious and disappear within a few days. Your doctor will advise you on how you should gradually discontinue Venlafaxine treatment and if you experience any of these or other symptoms which are troublesome, return to your doctor for further advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Venlafaxine tablets can cause side effects, although not everybody gets them. Usually they are not serious and do not last for long.

Serious Side Effects:
You should tell your doctor immediately if you have:

- an allergic reaction such as skin rash, swollen face or tongue, or shortness of breath or difficulty breathing.
- Neuroleptic malignant syndrome (symptoms may include extremely high body temperature, heavy sweating, fast heart rate, fast respiratory rate, fluctuating blood pressure, impaired consciousness, tremor, rigid, stiff muscles and stupor).

Muscles:
Common – joint or muscle pain
Uncommon – muscle spasm
Very rare – rhabdomyolysis (a disease which includes muscle pain, weakness and passing of dark red urine)

Neurological disorders:
Very common – dizziness, dry mouth, difficulty sleeping, nervousness and feeling tired
Common – abnormal dreams, agitation, anxiety, confusion, increased muscle tension, pins and needles, tremor
Uncommon – hallucinations, stiff muscles
Rare – clumsiness or loss of balance or co-ordination, slurring or difficulty speaking, jerky uncontrolled movements, seizures, Serotonergic syndrome (symptoms may include fever, agitation, confusion, muscle spasms or twitching, tremor, shivering and diarrhoea).
Very rare – feeling delirious
Kidney and urinary disorders:
Common – the need to go to the toilet more often
Uncommon – difficulty in urinating

Reproductive system and breast disorders:
Very common – abnormal ejaculation/orgasm
Common – reduced sex drive, impotence, menstrual disturbances in women
Rare – abnormal breast milk production

Breathing and chest (Respiratory disorders):
Common – shortness of breath, yawning
Very rare – pulmonary eosinophilia (lung changes - detected by a chest x-ray)

Skin:
Very common – sweating (including night sweats)
Common – itchy skin, rash
Uncommon – skin eruptions, reddening of the skin, sensitivity to light, hair loss
Rare – erythema multiforme, Stevens Johnson syndrome (these are both rare but serious skin conditions)

Special senses:
Common – abnormal or blurred vision, ringing in the ears
Uncommon – altered sensation of taste

- mania or hypomania (feeling 'high' or very over excited).

Very common: more than 1 in 10 people
Common: less than 1 in 10 people
Uncommon: less than 1 in 100 people
Rare: less than 1 in 1,000 people
Very rare: less than 1 in 10,000 people

Blood (Blood disorders):
Uncommon – bruising, bleeding
Rare – prolonged bleeding time, unusual bleeding
Very Rare – changes to your blood picture (blood count) – your doctor may take a blood test if concerned

Heart (Cardiac disorders):
Common – high blood pressure, palpitations, flushing
Uncommon – low blood pressure when standing, dizziness, irregular heart beat, fainting
Very rare – heart problems which may cause abnormal heart beats, chest pains and shortness of breath

Stomach and bowels (Gastrointestinal):
Very common - constipation, feeling sick
Common – anorexia, diarrhoea, indigestion, being sick
Uncommon – teeth clenching
Rare – bleeding of the stomach which may cause black, tarry stools
Very Rare – inflammation of the pancreas which may cause nausea, vomiting, stomach and back pain

General disorders:
Very common – weakness, headache
Common – stomach pain, chills, fever

Nutritional disorders:
Common – raised cholesterol levels, weight gain or loss
Uncommon – low blood sodium levels including Syndrome of Inappropriate Antidiuretic Hormone secretion (a syndrome of excessive levels of antidiuretic hormones [hormones that help the kidneys, and body, conserve the correct amount of water], which causes the body to retain water and certain levels of electrolytes in the blood to fall [such as sodium]), high liver enzyme levels
Rare – inflammation of the liver (hepatitis)
Very rare – increased prolactin levels in the blood (a hormone which stimulates breast milk production)

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

5. HOW TO STORE VENLAFAXINE TABLETS

No special storage instructions
Keep out of the reach and sight of children
Do not use after the expiry date stated on the carton.
Medicines should not be disposed of via the wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Venlafaxine tablets contain:
- The active substance is venlafaxine hydrochloride. Each tablet contains 25mg, 37.5mg, 50mg or 75mg of venlafaxine respectively.
- The other ingredients are lactose monohydrate, **cellulose** microcrystalline, **croscarmellose sodium, povidone K30,** magnesium stearate, hypromellose 6cP, titanium dioxide (E171), macrogol/PEG 400, Sunset yellow FCF lake (E110).

What Venlafaxine tablets look like and contents of the pack:
Venlafaxine 25mg tablets are orange, round biconvex, film-coated tablets, marked with V1.
Venlafaxine 37.5 mg tablets are orange, round, biconvex, film-coated tablets marked with V2.
Venlafaxine 50 mg tablets are orange, round, biconvex, film-coated tablets marked with V3.
Venlafaxine 75 mg tablets are orange, round, biconvex, film-coated tablets marked with V4 with a scoreline.
Venlafaxine tablets come in pack sizes of: 14, 28, 30, 42 and 56 tablets, packed into blister packs or plastic containers

Marketing Authorisation Holder
Olinka (UK) Limited, 38/40 Chamberlayne Road, London NW10 3JN

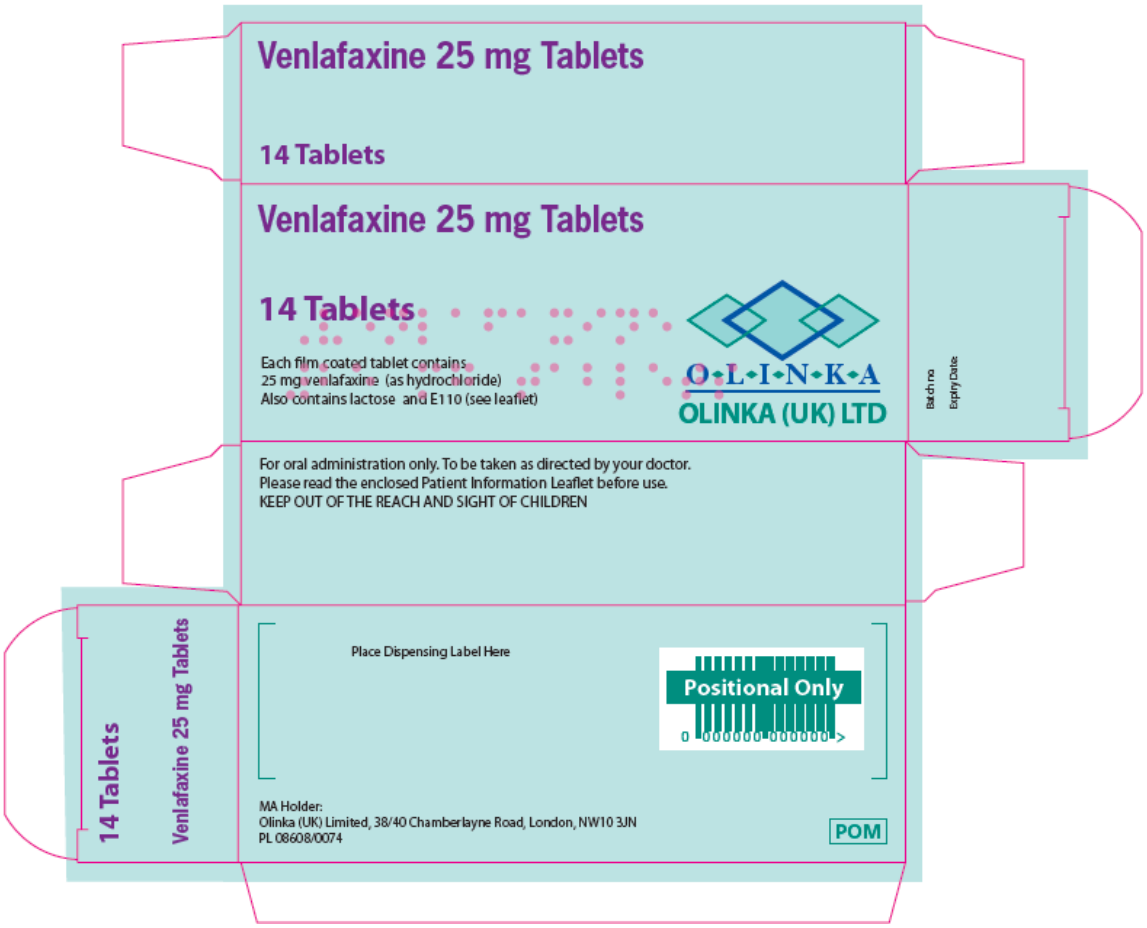
Manufacturer
Actavis Hf, Reykjavikurvegur 78, 220 Hafnarfjordur, Iceland.

This leaflet was last revised April 2008

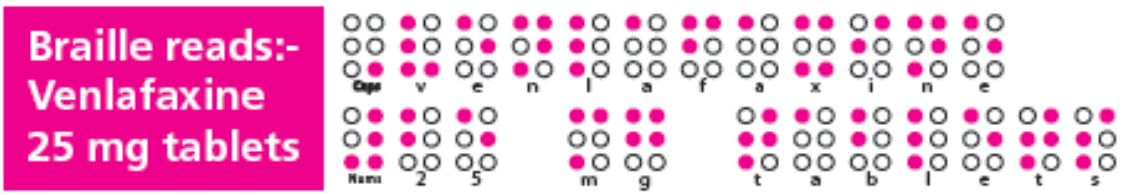
LABELLING

Venlafaxine 25mg tablets – PL 08608/0074 (labelling for 0078 and 0082 is identical apart from PL number)

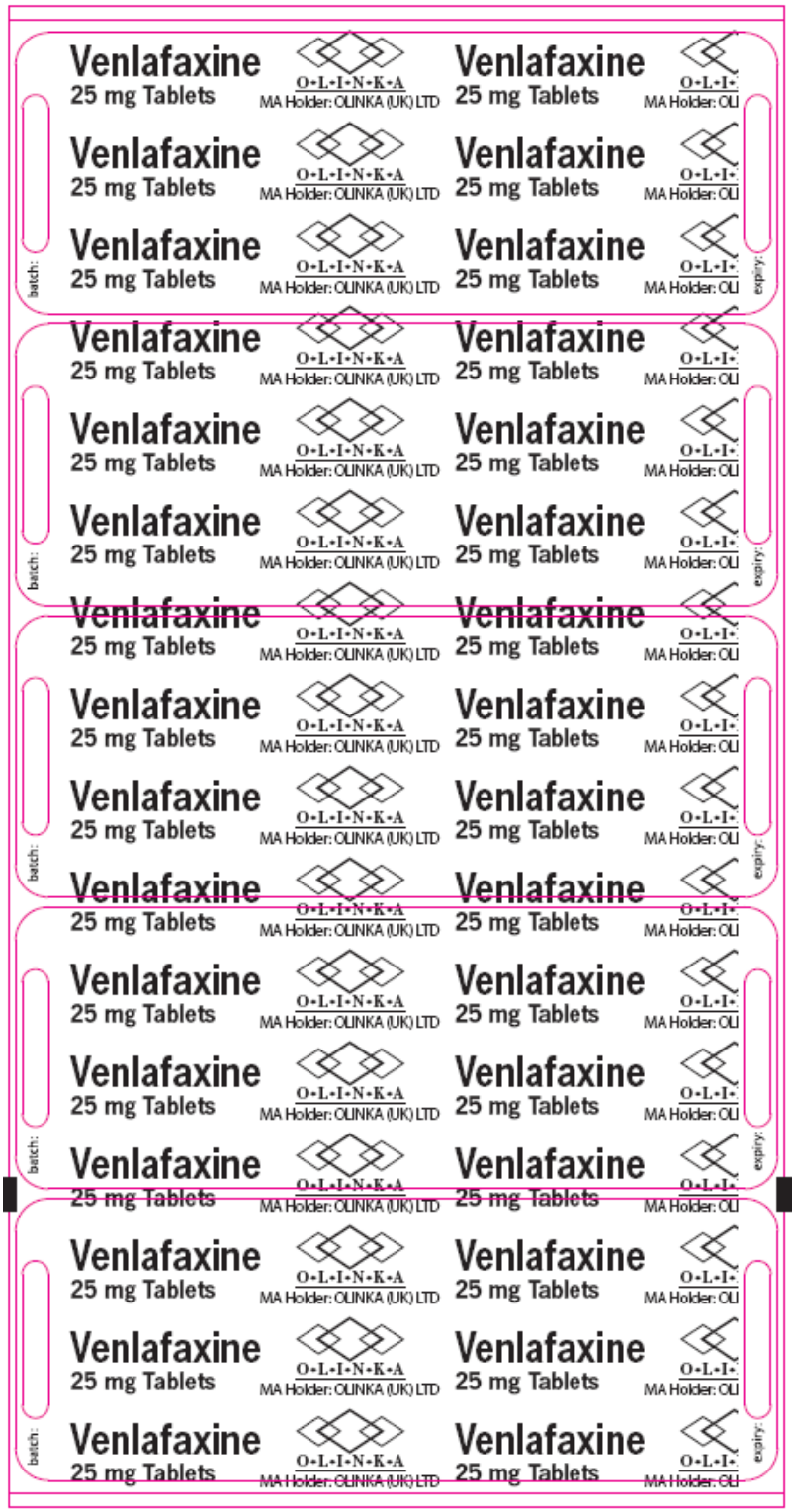
Carton for blisters, with braille



Braille translation

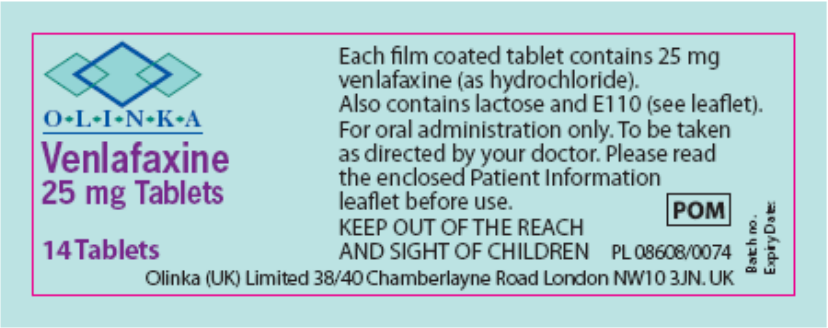


Blister foils



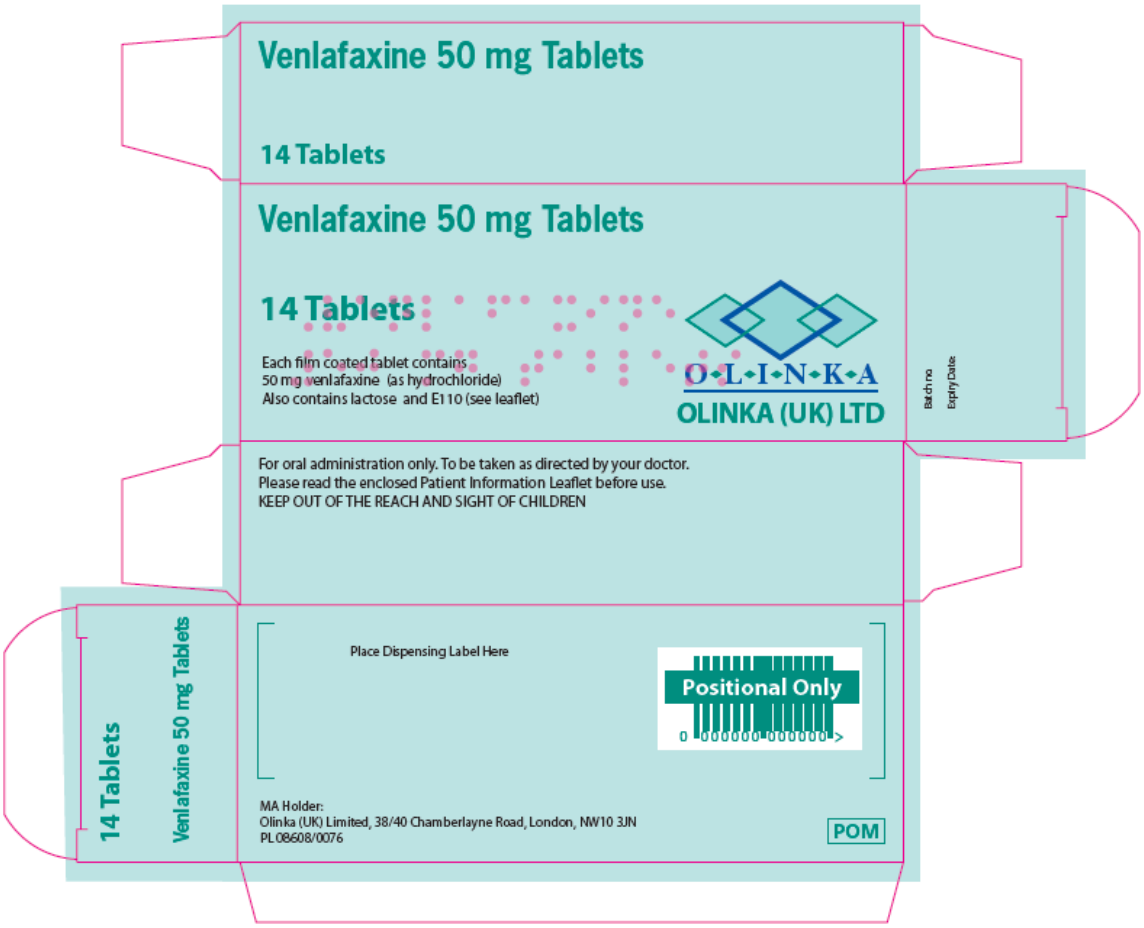
Carton for HDPE container, with braille

Label for HDPE container

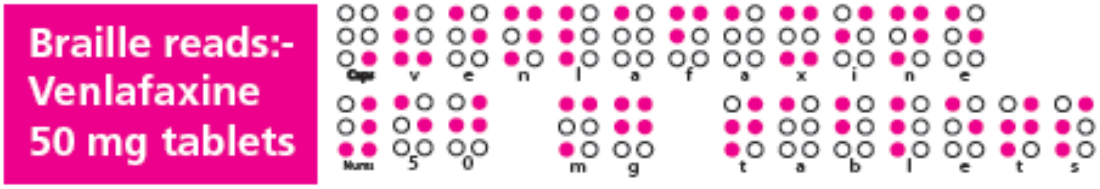


Venlafaxine 50mg tablets – PL 08608/0076 (labelling for 0080 and 0084 is identical apart from PL number)

Carton for blisters, with braille



Braille translation



Blister foils


Venlafaxine
50 mg Tablets
O•L•I•N•K•A
MA Holder: OLINKA (UK) LTD
batch:
expiry:

Carton for HDPE container, with braille

Label for HDPE container