

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION
HOLDERS IN THE MEMBER STATES**

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>(Invented) name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Austria	Wyeth-Lederle Pharma GmbH Storchengasse 1 1150 Vienna Austria	Efectin 50 mg - Tabletten	50 mg	Tablets	Oral use
Cyprus	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	Efexor	37.5 mg	Tablets	Oral use
Cyprus	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	Efexor	50 mg	Tablets	Oral use
Cyprus	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	Efexor	75 mg	Tablets	Oral use
Denmark	John Wyeth & Brother Ltd. New Lane Havant, Hants PO9 2NG United Kingdom	Efexor	37.5 mg	Tablets	Oral use
Finland	John Wyeth & Brothers Ltd, New Lane, Havant, HANTS, P09 2NG United Kingdom	Efexor	37.5 mg	Tablets	Oral use
Finland	John Wyeth & Brothers Ltd, New Lane, Havant, HANTS, P09 2NG United Kingdom	Efexor	75 mg	Tablets	Oral use

France	Wyeth Pharmaceuticals France Coeur Défense - Tour A - La Défense 4 92931 Paris La Défense Cedex, France	Effexor	25 mg	Tablets	Oral use
France	Wyeth Pharmaceuticals France Coeur Défense - Tour A - La Défense 4 92931 Paris La Défense Cedex, France	Effexor	50 mg	Tablets	Oral use
France	Wyeth Pharmaceuticals France Coeur Défense - Tour A - La Défense 4 92931 Paris La Défense Cedex, France	Trevilor	50 mg	Tablets	Oral use
Germany	Wyeth Pharma GmbH Wienburgstrasse 207, D-48159 Muenster Germany	Trevilor Tabletten 25mg	25 mg	Tablets	Oral use
Germany	Wyeth Pharma GmbH Wienburgstrasse 207, D-48159 Muenster Germany	Trevilor Tabletten 37.5mg	37.5 mg	Tablets	Oral use
Germany	Wyeth Pharma GmbH Wienburgstrasse 207, D-48159 Muenster Germany	Trevilor Tabletten 50mg	50 mg	Tablets	Oral use
Germany	Wyeth Pharma GmbH Wienburgstrasse 207, D-48159 Muenster Germany	Trevilor Tabletten 75mg	75 mg	Tablets	Oral use
Greece	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	EFEXOR	25 mg	Tablets	Oral use

Greece	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	EFEXOR	37,5 mg	Tablets	Oral use
Greece	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	EFEXOR	50 mg	Tablets	Oral use
Greece	Wyeth Hellas S.A. 126, Kyprou & 25th Martiou str., 164 52 Argyroupolis-Athens, Greece	EFEXOR	75 mg	Tablets	Oral use
Iceland	John Wyeth & Brothers Ltd New Lane, Havant, HANTS, P09 2NG United Kingdom	Efexor	37.5 mg	Tablets	Oral use
Ireland	John Wyeth & Brother Ltd trading as Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	37.5 mg	Tablets	Oral use
Ireland	John Wyeth & Brother Ltd trading as Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	75 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Efexor	25 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Efexor	37.5 mg	Tablets	Oral use

Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Efexor	50 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Efexor	75 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Faxine	37.5 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Faxine	50 mg	Tablets	Oral use
Italy	Wyeth Medica Ireland Little Connell – Newbridge, Co. Kildare Ireland	Faxine	75 mg	Tablets	Oral use
Malta	John Wyeth & Brother Ltd trading as Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, United Kingdom	Efexor	37.5 mg	Tablets	Oral use
Malta	John Wyeth & Brother Ltd trading as Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, United Kingdom	Efexor	75 mg	Tablets	Oral use
Norway	John Wyeth & Brothers Ltd New Lane, Havant, HANTS, P09 2NG, United Kingdom	Efexor	37.5 mg	Tablets	Oral use

Spain	WYETH FARMA S.A. Ctra. De Burgos Km 23 Desvio Algete, 28700 San Sebastian de los Reyes Spain	VANDRAL 37,5 mg comprimidos	37.5 mg	Tablets	Oral use
Spain	WYETH FARMA S.A. Ctra. De Burgos Km 23 Desvio Algete, 28700 San Sebastian de los Reyes Spain	VANDRAL 50 mg comprimidos	50 mg	Tablets	Oral use
Spain	WYETH FARMA S.A. Ctra. De Burgos Km 23 Desvio Algete, 28700 San Sebastian de los Reyes Spain	VANDRAL 75 mg comprimidos	75 mg	Tablets	Oral use
Spain	Laboratorios Almirall, S.A. General Mitre, 151 08022 Barcelona Spain	Dobupal 37,5 mg comprimidos	37.5 mg	Tablets	Oral use
Spain	Laboratorios Almirall, S.A. General Mitre, 151 08022 Barcelona Spain	Dobupal 50 mg comprimidos	50 mg	Tablets	Oral use
Spain	Laboratorios Almirall, S.A. General Mitre, 151 08022 Barcelona Spain	Dobupal 75 mg comprimidos	75 mg	Tablets	Oral use
United Kingdom	John Wyeth & Brother Limited, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	25 mg	Tablets	Oral use
United Kingdom	John Wyeth & Brother Limited, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	37.5 mg	Tablets	Oral use

United Kingdom	John Wyeth & Brother Limited, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	50 mg	Tablets	Oral use
United Kingdom	John Wyeth & Brother Limited, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH United Kingdom	Efexor	75 mg	Tablets	Oral use

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES
OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET
PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF EFEXOR AND ASSOCIATED NAMES (SEE ANNEX I)

Efexor has been included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names), the European Commission notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across the EU.

The following Sections of the Product Information were addressed during this harmonisation procedure.

SPC Section 4.1 - Therapeutic Indications

Following the European Commission's request, Section 4.1 of the Summary of Product Characteristics was harmonised to include the following therapeutic indications as worded and described below:

- "*treatment of major depressive episodes*", with no inclusion of references to associated anxiety, given that the studies designed to investigate the anxiolytic effect of venlafaxine revealed that it is difficult to distinguish anxiety from the concomitant depression disorder;

- "*prevention of recurrence of major depressive episodes*", which was adequately supported by the data provided. (The "*prevention of relapse of depression*" indication was excluded since, based on current EU guidelines, the relapse indication is encompassed when approval for the indication of major depressive episodes is granted). A minority of CHMP members were of the opinion that this indication should be deleted from section 4.1, and a statement should be included in section 4.2, to indicate that longer-term treatment may also be appropriate for prevention of recurrence of major depressive episodes.

SPC Section 4.2 - Posology and Method of Administration

The MAH was asked to harmonize the following posology texts in the SPC:

- limitations of treatment duration of the maximum daily dose of 375mg to 4 weeks;
- differences in maximum recommended daily dose.

Major Depressive Episodes: the CHMP considered that the maximum dose of 375mg/day Efexor is safe and effective in a long term perspective and recommended that it is approved without duration limitations in the harmonised SPC.

Use in elderly patients: based on published data raising the possibility of renal impairment and the potential for changes in neurotransmitter sensitivity and affinity with aging, a new wording for use in elderly patients was agreed in the SPC. It was agreed that "*No specific dose adjustments are considered necessary based on patient age alone*". However, a recommendation to exercise caution in treating elderly patients, to use the lowest effective dose and to monitor carefully elderly patients when an increase in the dose is required was also included in the harmonized SPC.

Use in children and adolescents under the age of 18 years: it was agreed that "*Venlafaxine is not recommended for use in children and adolescents*". Furthermore, a statement was included in the harmonized SPC to highlight that controlled studies in children did not demonstrate efficacy of venlafaxine in the "major depressive disorder" indication.

Use in patients with hepatic impairment: it was agreed to recommend in the SPC the individualization of dosage to overcome clearance variability between patients with hepatic impairment.

Use in patients with renal impairment: it was agreed that the individualisation of the dosage may be desirable, and this concept was introduced in the text for harmonisation.

Withdrawal symptoms seen on discontinuation of venlafaxine: based on a proposed text for the SPC for Selective Serotonin Reuptake Inhibitors (SSRIs) / Selective Norepinephrine Reuptake Inhibitors (SNRIs) (Sections 4.2, 4.4, and 4.8) reviewed by the Pharmacovigilance Working Party, it was agreed to incorporate this text into the harmonised SPC.

SPC Section 4.3 - Contraindications

The MAH was asked to harmonize Section 4.3, for which the following differences between SPCs needed to be evaluated

- Monoamine oxidase inhibitors (MAOIs);
- Cardiovascular safety
- Uncontrolled hypertension.

The MAH was of the view that all MAOIs should be contraindicated with venlafaxine. However, the CHMP considered that only non-selective, irreversible MAOIs should be contraindicated and that a strong warning in Section 4.4 and Section 4.5 of the SPC should be sufficient for the reversible MAOIs. The SPC was amended to reflect the CHMP position.

A new study report was provided which concluded that the use of venlafaxine was not associated with an excess risk of sudden cardiac death compared with the SSRIs fluoxetine and citalopram or duloxetine in patients with depression or anxiety. With regards to cardiovascular safety, it was agreed that a contraindication was not warranted and that a revised wording for Section 4.4 was sufficient.

The MAH was of the view that a contraindication in patients with uncontrolled hypertension was not warranted. Given that strong warnings recommending the monitoring of blood pressure for all patients prior to the initiation of treatment were included in Section 4.4, the CHMP agreed that a contraindication in patients with uncontrolled hypertension was not warranted.

SPC Section 4.4 - Special Warnings and Precautions for Use

The MAH was asked to harmonize Section 4.4, for which the following differences between SPCs needed to be evaluated:

- the mentioning of reports of aggression in relation to starting and discontinuing treatment;
- treatment of children and adolescents under the age of 18, which was recommended by the CHMP in 2005 to be included in Section 4.4 of the SPC (Commission Decision of 19-VIII-2005);

With regards to the aggression reports, it was agreed to introduce a wording to indicate that aggression may occur in patients receiving venlafaxine, under initiation, dose changes and discontinuation of treatment.

A warning on the use of Efexor in the treatment of children and adolescents under the age of 18 years was also agreed upon and introduced in Section 4.4.

SPC Section 4.5 - Interaction with other medicinal products and other forms of interaction

The MAH was asked to harmonise Section 4.5 in the Summary of Product Characteristics, for which the following differences between SPCs needed to be evaluated:

- monoamine oxidase inhibitors.

The MAH wished to maintain that all MAOIs should be contraindicated whereas the CHMP considered that only non-selective, irreversible MAOIs should be contraindicated and that a strong warning in Section 4.5 of the SPC should be sufficient for the reversible MAOIs. The SPC was amended according to the CHMP position. In the harmonized text of Section 4.4 it is indicated that non-selective MAOIs should not be given concomitantly, and that reversible, selective MAOIs such as moclobemide are not recommended in combination with venlafaxine, due to the risk of serotonin syndrome.

SPC Section 4.8 - Undesirable effects

The MAH was asked to identify differences between the listed adverse events in the nationally approved SPCs and the MAH's CDS, and to organise Section 4.8 according to the MedDRA system organ class. The MAH completed both the assessment of urinary disorders and of occurrence of gastrointestinal haemorrhage and agreed to add them to the adverse reaction table. Psychomotor restlessness was also added to the table of adverse drug reactions. Following review, chills, confusion, depersonalisation, headache, menstrual disorders, palpitations and pollakiuria were included in this table. The MAH did not agree with the PhVWP/CMD(h) agreed SPC wording for all antidepressants for Section 4.8, since suicidal ideation is not considered an adverse reaction in adult patients, but agreed to comply with the mandated class labelling.

GROUNDINGS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling, package leaflet.

- the Summaries of Products Characteristic, labelling, package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Efexor and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 25 mg tablets
Efexor and associated names (see Annex I) 37.5 mg tablets
Efexor and associated names (see Annex I) 50 mg tablets
Efexor and associated names (see Annex I) 75 mg tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see [section 6.1](#).

3. PHARMACEUTICAL FORM

Tablet.

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

4.2 Posology and method of administration

Major depressive episodes

The recommended starting dose of immediate-release venlafaxine is 75 mg/day in two or three divided doses taken with food. Patients not responding to the initial 75 mg/day dose may benefit from dose increases up to a maximum dose of 375 mg/day. Dosage increases can be made at intervals of 2 weeks or more. If clinically warranted due to symptom severity, dose increases can be made at more frequent intervals, but not less than 4 days.

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

Patients should be treated for a sufficient period of time, usually several months or longer. Treatment should be reassessed regularly on a case-by-case basis. Longer-term treatment may also be appropriate

for prevention of recurrence of major depressive episodes (MDE). In most of the cases, the recommended dose in prevention of recurrence of MDE is the same as the one used during the current episode.

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

Use in elderly patients

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

Use in children and adolescents under the age of 18 years

Venlafaxine is not recommended for use in children and adolescents.

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

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

Use in patients with hepatic impairment

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

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

Use in patients with renal impairment

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

Withdrawal symptoms seen on discontinuation of venlafaxine

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

For oral use.

It is recommended that venlafaxine immediate-release tablets be taken with food, at approximately the same time each day.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

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

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

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

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

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

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

Use in children and adolescents under 18 years of age

Efexor should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for

the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Serotonin syndrome

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

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

Narrow-angle glaucoma

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

Blood pressure

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

Heart rate

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

Cardiac disease and risk of arrhythmia

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

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

Convulsions

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

Hyponatraemia

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

Abnormal bleeding

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

Serum cholesterol

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

Co-administration with weight loss agents

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

Mania/hypomania

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

Aggression

Aggression may occur in a small number of patients who have received antidepressants, including venlafaxine. This has been reported under initiation, dose changes and discontinuation of treatment.

As with other antidepressants, venlafaxine should be used cautiously in patients with a history of aggression.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation (tapering and post-tapering) occurred in approximately 35% of patients treated with venlafaxine and 17% of patients taking placebo.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that venlafaxine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Akathisia/psychomotor restlessness

The use of venlafaxine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Dry mouth

Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

Lactose intolerance

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

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOI)

Irreversible non-selective MAOIs

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

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of venlafaxine with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before initiation of venlafaxine

treatment. It is recommended that venlafaxine should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

Reversible, non-selective MAOI (linezolid)

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

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

Serotonin syndrome

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

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

CNS-active substances

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

Ethanol

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

Effect of other medicinal products on venlafaxine

Ketoconazole (CYP3A4 inhibitor)

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

Effect of venlafaxine on other medicinal products

Lithium

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

Diazepam

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

Imipramine

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

Haloperidol

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

Risperidone

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

Metoprolol

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

Indinavir

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

4.6 Pregnancy and lactation

Pregnancy

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

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

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

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

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Body System	Very Common	Common	Uncommon	Rare	Not Known
Haematological/ Lymphatic			Ecchymosis, Gastrointestinal haemorrhage		Mucous membrane bleeding, Prolonged bleeding time, Thrombocytopaenia, Blood dyscrasias, (including agranulocytosis, aplastic anaemia, neutropaenia and pancytopaenia)
Metabolic/ Nutritional		Serum cholesterol increased, Weight loss	Weight gain		Abnormal liver function tests, Hyponatraemia, Hepatitis, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Prolactin increased
Nervous	Dry mouth (10.0%), Headache (30.3%)*	Abnormal dreams, Decreased libido, Dizziness, Increased muscle tonus (hypertonia), Insomnia, Nervousness, Paresthesia, Sedation, Tremor, Confusion, Depersonalisation	Apathy, Hallucinations, Myoclonus, Agitation, Impaired coordination and balance	Akathisia/ Psychomotor restlessness, Convulsion, Manic reaction	Neuroleptic Malignant Syndrome (NMS), Serotonergic syndrome, Delirium, Extrapyramidal reactions (including dystonia and dyskinesia), Tardive dyskinesia, Suicidal ideation and behaviours**
Special Senses		Abnormality of accommodation, Mydriasis, Visual disturbance,	Altered taste sensation, Tinnitus		Angle-closure glaucoma
Cardiovascular		Hypertension, Vasodilatation (mostly hot flashes/flushes), Palpitations	Postural hypotension, Syncope, Tachycardia		Hypotension, QT prolongation, Ventricular fibrillation, Ventricular tachycardia (including torsade de pointes)
Respiratory		Yawning			Pulmonary eosinophilia
Digestive	Nausea (20.0%)	Appetite decreased (anorexia), Constipation, Vomiting	Bruxism, Diarrhoea		Pancreatitis

Body System	Very Common	Common	Uncommon	Rare	Not Known
Skin	Sweating (including night sweats) [12.2%]		Rash, Alopecia		Erythema multiforme, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus, Urticaria
Musculoskeletal					Rhabdomyolysis
Urogenital		Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction (impotence), Urination impaired (mostly hesitancy), Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g., menorrhagia, metrorrhagia), Pollakiuria	Abnormal orgasm (females), Urinary retention		
Body as a Whole		Asthenia (fatigue), Chills	Photosensitivity reaction		Anaphylaxis

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

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

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

Paediatric patients

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

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

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

4.9 Overdose

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

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

Recommended treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H₁-histaminergic or α_1 -adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicinal products, such as anticholinergic, sedative and cardiovascular side effects.

Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

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

Major depressive episodes

The efficacy of venlafaxine immediate-release as a treatment for major depressive episodes was demonstrated in five randomised, double-blind, placebo-controlled, short-term trials ranging from 4 to 6 weeks duration, for doses up to 375 mg/day. The efficacy of venlafaxine prolonged-release as a treatment for major depressive episodes was established in two placebo-controlled, short-term studies for 8 and 12 weeks duration, which included a dose range of 75 to 225 mg/day.

In one longer-term study, adult outpatients who had responded during an 8-week open trial on venlafaxine prolonged-release (75, 150, or 225 mg) were randomised to continuation of their same venlafaxine prolonged-release dose or to placebo, for up to 26 weeks of observation for relapse.

In a second longer-term study, the efficacy of venlafaxine in prevention of recurrent depressive episodes for a 12-month period was established in a placebo-controlled double-blind clinical trial in adult outpatients with recurrent major depressive episodes who had responded to venlafaxine treatment (100 to 200 mg/day, on a b.i.d. schedule) on the last episode of depression.

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Special populations

Age and gender

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

CYP2D6 extensive/poor metabolisers

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

Patients with hepatic impairment

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

Patients with renal impairment

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

Not all pack sizes may be marketed.

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

MM/YYYY

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE/TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 25 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

See the package leaflet for further information.

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE/TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 37.5 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

See the package leaflet for further information.

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE/TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 50 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

See the package leaflet for further information.

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/BOTTLE/TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 75 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

See the package leaflet for further information.

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 25 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 37.5 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 50 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Efexor and associated names (see Annex I) 75 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Efexor and associated names (see Annex I) 25 mg tablets
Efexor and associated names (see Annex I) 37.5 mg tablets
Efexor and associated names (see Annex I) 50 mg tablets
Efexor and associated names (see Annex I) 75 mg tablets

[See Annex I - To be completed nationally]

Venlafaxine

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

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

In this leaflet:

1. What Efexor is and what is used for
2. Before you take Efexor
3. How to take Efexor
4. Possible side effects
5. How to store Efexor
6. Further information

1. WHAT EFEXOR IS AND WHAT IT IS USED FOR

Efexor is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression and other conditions, such as anxiety disorders. It is thought that people who are depressed and/or anxious have lower levels of serotonin and noradrenaline in the brain. It is not fully understood how antidepressants work, but they may help by increasing the levels of serotonin and noradrenaline in the brain.

Efexor is a treatment for adults with depression. Treating depression properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and more difficult to treat.

2. BEFORE YOU TAKE EFEXOR

Do not take Efexor

- If you are allergic to venlafaxine or any of the other ingredients of Efexor.
- If you are also taking or have taken any time within the last 14 days any medicines known as irreversible monoamine oxidase inhibitors (MAOIs), used to treat depression or Parkinson's disease. Taking an irreversible MAOI together with other medicines, including Efexor, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Efexor before you take any irreversible MAOI (see also the sections "Serotonin syndrome" and "Taking other medicines").

Take special care with Efexor

- If you use other medicines that taken concomitantly with Efexor could increase the risk of developing serotonin syndrome (see the section “Taking other medicines”).
- If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- If you have a history of high blood pressure.
- If you have a history of heart problems.
- If you have a history of fits (seizures).
- If you have a history of low sodium levels in your blood (hyponatraemia).
- If you have a tendency to develop bruises or a tendency to bleed easily (history of bleeding disorders), or if you are taking other medicines that may increase the risk of bleeding.
- If your cholesterol levels get higher.
- If you have a history of, or if someone in your family has had, mania or bipolar disorder (feeling over-excited or euphoric).
- If you have a history of aggressive behaviour.

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

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

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 you first start taking antidepressants, since these medicines all take time to work, usually about two weeks, but sometimes longer.

You may be more likely to think like this:

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

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed 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.

Dry mouth

Dry mouth is reported in 10% of patients treated with venlafaxine. This may increase the risk of caries. Therefore, you should take special care in your dental hygiene.

Use in children and adolescents under 18 years of age

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

Taking other medicines

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

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

Do not start or stop taking any medicines, including those bought without a prescription, natural and herbal remedies, before checking with your doctor or pharmacist.

- Monoamine oxidase inhibitors (MAOIs: see the section “Before you take Efexor”).
- Serotonin syndrome:
- Serotonin syndrome, a potentially life-threatening condition (see the section “Possible Side Effects”), may occur with venlafaxine treatment, particularly when taken with other medicines. Examples of these medicines include:
- Triptans (used for migraine)
- Medicines to treat depression, for instance SNRI, SSRIs, tricyclics, or medicines containing lithium
- Medicines containing linezolid, an antibiotic (used to treat infections)
- Medicines containing moclobemide, a reversible MAOI (used to treat depression)
- Medicines containing sibutramine (used for weight loss)
- Medicines containing tramadol (a pain-killer)
- Products containing St. John’s Wort (also called *Hypericum perforatum*, a natural or herbal remedy used to treat mild depression)
- Products containing tryptophan (used for problems such as sleep and depression)

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

The following medicines may also interact with Efexor and should be used with caution. It is especially important to mention to your doctor or pharmacist if you are taking medicines containing:

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

Taking Efexor with food and drink

Efexor should be taken with food (see section 3 “HOW TO TAKE EFEXOR”).

You should avoid alcohol while you are taking Tradename.

Pregnancy and breast-feeding

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

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

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

Driving and using machines

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

Important information about some of the ingredients of Efexor

[To be completed nationally]

3. HOW TO TAKE EFEXOR

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

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

Take Efexor at approximately the same time each day, in the morning and in the evening.

Efexor should be taken with food.

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

Do not stop taking Efexor without talking to your doctor (see the section “If you stop taking Efexor”).

If you take more Efexor than you should

Call your doctor or pharmacist immediately if you take more than the amount of Efexor prescribed by your doctor.

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

If you forget to take Efexor

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

If you stop taking Efexor

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

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Efexor can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not take more Efexor. Tell your doctor immediately, or go to the casualty department at your nearest hospital:

- Chest tightness, wheezing, trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, dizziness, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)
-

Serious side effects

If you notice any signs of the following, you may need urgent medical attention:

- Heart problems, such as fast or irregular heart rate, increased blood pressure
- Eye problems, such as blurred vision, dilated pupils
- Nerve problems, such as dizziness, pins and needles, movement disorder, seizures or fits
- Psychiatric problems, such as hyperactivity and euphoria
- Treatment withdrawal (see the section “HOW TO TAKE EFEXOR, If you stop taking Efexor”)

Complete side effect listing

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

Very common	Affects more than 1 user in 10
Common	Affects 1 to 10 users in 100
Uncommon	Affects 1 to 10 users in 1,000
Rare	Affects 1 to 10 users in 10,000
Not known	Frequency cannot be estimated from the available data

- **Blood disorders**

Uncommon: bruising; black tarry stools (faeces) or blood in stools, which can be a sign of internal bleeding

Not known: reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding; blood disorders which may lead to an increased risk of infection

- **Metabolism/nutritional disorders**

Common: weight loss; increased cholesterol

Uncommon: weight gain

Not known: slight changes in blood levels of liver enzymes; decrease in blood sodium levels; itchiness, yellow skin or eyes, dark urine, or flu-like symptoms, which are symptoms of inflammation of the liver (hepatitis); confusion, excessive water intake (known as SIADH); abnormal breast milk production

- **Nervous system disorders**

Very common: dry mouth; headache

Common: abnormal dreams; decreased libido; dizziness; increased muscle tonus; insomnia; nervousness; pins and needles; sedation; tremor; confusion; feeling separated (or detached) from yourself and reality

Uncommon: lack of feeling or emotion; hallucinations; involuntary movement of the muscles; agitation; impaired coordination and balance

Rare: a sensation of restlessness or an inability to sit or stand still; seizures or fits; feeling over-excited or euphoric

Not known: a high temperature with rigid muscles, confusion or agitation, and sweating, or if you experience jerky muscle movements which you can't control, these may be symptoms of serious conditions known as neuroleptic malignant syndrome; euphoric feelings, drowsiness, sustained rapid eye movement, clumsiness, restlessness, feeling of being drunk, sweating or rigid muscles, which are symptoms of serotonergic syndrome; disorientation and confusion often accompanied by hallucination (delirium); stiffness, spasms and involuntary movements of the muscles; thoughts of harming or killing yourself

- **Sight and hearing disorders**

Common: blurred vision

Uncommon: altered taste sensation; ringing in the ears (tinnitus)

Not known: severe eye pain and decreased or blurred vision

- **Heart or circulation disorders**

Common: increase in blood pressure; flushing; palpitations

Uncommon: feeling dizzy (particularly when standing up too quickly), fainting, fast heartbeat

Not known: decrease in blood pressure; abnormal, rapid or irregular heart beat, which could lead to fainting

- **Breathing disorders**

Common: yawning

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

- **Digestive disorders**

Very common: nausea

Common: appetite decreased; constipation; vomiting

Uncommon: grinding of the teeth; diarrhoea

Not known: severe abdominal or back pains (which could indicate a serious problem in the gut, liver or pancreas)

- **Skin disorders**

Very common: sweating (including night sweats)

Uncommon: rash; abnormal hair loss

Not known: skin rash, which may lead to severe blistering and peeling of the skin; itching; mild rash

- **Muscle disorders**

Not known: unexplained muscle pain, tenderness or weakness (rhabdomyolysis)

- **Urinary system disorders**

Common: difficulties passing urine; increased frequency in urination

Uncommon: inability to pass urine

- **Reproductive and sexual disorders**

Common: abnormal ejaculation/orgasm (males); lack of orgasm; erectile dysfunction

(impotence); menstrual irregularities such as increased bleeding or increased irregular bleeding

Uncommon: abnormal orgasm (females)

- **General**

Common: weakness (asthenia); chills

Uncommon: sensitivity to sunlight

Not known: swollen face or tongue, shortness of breath or difficulty breathing, often with skin rashes (this may be a serious allergic reaction)

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

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

5. HOW TO STORE EFEXOR

Keep out of the reach and sight of children.

Do not use Efexor after the expiry date, which is stated on the packaging.

[To be completed nationally]

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

6. FURTHER INFORMATION

What Efexor contains

The active substance is venlafaxine.

[To be completed nationally]

What Efexor looks like and contents of the pack

[To be completed nationally]

Tablet

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Efectin 50 mg -Tabletten
Cyprus, Denmark, Finland, Greece, Iceland, Ireland, Malta, Norway, United Kingdom	Efexor
France	Effexor Trevilor
Germany	Trevilor Tabletten 25 mg Trevilor Tabletten 37.5 mg Trevilor Tabletten 50 mg Trevilor Tabletten 75 mg
Italy	Efexor Faxine
Spain	Vandral 37,5 mg comprimidos Vandral 50 mg comprimidos Vandral 75 mg comprimidos

*[Please note that not all listed products and strengths may be available.]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]