Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Efexor 75 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg of venlafaxine (as hydrochloride).

Excipients: Lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Products imported from Spain:
Peach coloured, oblong tablet, plain with a breakline on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Efexor is indicated for the treatment of depressive illness in both hospitalised patients and outpatients, including depression accompanied by anxiety.

Following an initial response Efexor 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

Adults:
The usual recommended dose is 75mg per day given in two divided doses (37.5mg twice daily). If, after several weeks, further clinical improvement is required, the dose may be increased to 150mg per day given in two divided doses (75mg twice daily).

If, in the judgement of the physician, a higher dose is required, for example in more severely depressed or hospitalised patients, a starting dose of 150mg per day may be given in two divided doses (75mg twice daily). The daily dose may then be increased by up to 75mg every two or three days until the desired response is achieved. The maximum recommended dose is 375mg per day. The dose should then be gradually reduced to the usual dosage, consistent with patient response and tolerance.

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.

It is recommended that Efexor be taken with food.

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

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

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

Elderly Patients:
No adjustment in the usual dosage is recommended for elderly patients. In a trial investigating the kinetics of venlafaxine in the elderly, the half-life (at steady-state conditions) was prolonged by 1-2 hours, mainly in the male subjects. This was apparently due to an 18% reduction in the clearance of venlafaxine and O-desmethylvenlafaxine. The small increase in steady-state plasma levels of venlafaxine and O-desmethylvenlafaxine which resulted, was not judged to be clinically significant; no adjustment in dosage is necessary. However, as with any therapy, caution should be exercised in treating the elderly (eg. 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 Efexor in these patients *(see sections 4.3 Contra-indications and 4.8 Undesirable Effects).*

The efficacy and safety of Efexor 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 Efexor for the individual patient. It is generally agreed that acute episodes of major depression require several months or longer of sustained therapy. Efexor 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 Efexor:
Discontinuation effects are well known to occur with the abrupt withdrawal of other antidepressants. While withdrawal reactions with Efexor have not been systematically evaluated in controlled clinical trials, a retrospective survey of events occurring during taper or following discontinuation of Efexor revealed the following events that occurred at an incidence of at least 5% and at least twice the placebo incidence: fatigue, headache, nausea, dizziness, sleep disturbance and nervousness. Diarrhoea and one hypomanic episode was also reported.

In post-marketing experience, symptoms reported following discontinuation, dose reduction or tapering of venlafaxine at various doses have also included confusion, paraesthesia, sweating, vertigo and vomiting. It is therefore recommended that when discontinuing Efexor after more than one week's therapy, the dose should be gradually reduced over at least one week and the patient monitored in order to minimise the risk of withdrawal reactions.

The period required for discontinuation may depend on the dose, duration of therapy and the individual patient.

4.3 Contraindications

1. Known or suspected pregnancy.

2. Insufficient data are available to support the use of Efexor in lactating women. Therefore, such use is contra-indicated.

3. Known hypersensitivity to venlafaxine or any other component of the product.

4. Concomitant use of venlafaxine with monoamine oxidase inhibitors.
(See Interaction with other medicinal products and other forms of interaction).

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

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 Efexor 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.

1. The risk of suicide attempt must be considered in all depressed patients. The smallest quantity of tablets should be prescribed consistent with good patient management in order to reduce the possibility of overdose.

2. In clinical trials with venlafaxine tablets, seizures were reported in 0.2% of all venlafaxine-treated patients. All patients recovered. No seizures occurred in Efexor – treated patients during clinical trials.
However, as with all antidepressants, Efexor should be introduced with caution in patients with a history of seizure and should be discontinued in any patient developing a seizure.

3. During clinical trials, rash developed in 3% of patients treated with venlafaxine. Patients should be advised to notify their physician if they develop a rash, urticaria or a related allergic phenomenon.

4. Dose related increases in blood pressure have been reported in patients receiving venlafaxine. In all premarketing trials, 2.2% of venlafaxine treated patients were judged to have clinically significant blood pressure increases compared with 0.4% of placebo-treated patients. In general, patients treated with 200mg per day showed minor increases, while in a short-term dose-ranging study with Efexor tablets, the highest dose (300 to 375mg/day) was associated with mean increases in supine and diastolic blood pressure of approximately 4mmHg by week 4, and 7mmHg by week 6. 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 Efexor therapy.

5. 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 Efexor.

6. 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 ovserved 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.

7. 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.

8. The clearances of venlafaxine and its active metabolite are decreased and half-lives increased in patients with moderate to severe renal impairment or cirrhosis of the liver.
Therefore, Efexor should be used with caution in these patients. A lower or less frequent dose might be necessary in such patients as indicated above under "Posology and Method of Administration".

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

10. Cases of hypomatraemia and/or Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) may occur with venlafaxine, usually in volume-depleted or dehydrated patients, including patients taking diuretics and the elderly.

11. Women of childbearing potential should employ adequate contraception whilst taking Efexor.

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

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

14. As with serotonin-reuptake inhibitors, the risk of skin and mucous membrane bleeding may be increased in patients taking venlafaxine. Efexor should be used with caution in patients predisposed to bleeding at these sites.

15. ***Use in children and adolescents under the age of 18:***
Lustral should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicidal attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviours 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.

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, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Given these reactions reported with concomitant or immediately consecutive administration of MAOIs with other antidepressants with pharmacological properties similar to Efexor, do not use Efexor in combination with an MAOI, or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Efexor before starting an MAOI. *(See also Contraindications).*

Other CNS-active drugs:
The risk of using Efexor in combination with other CNS-active drugs has not been systematically evaluated, except in the cases described below. Consequently caution is advised if the concomitant administration of Efexor and other CNS-active drugs is required.

Lithium: The steady-state pharmacokinetics of venlafaxine administered at 150mg/day were not affected when a single 600mg oral dose of lithium was co-administered. O-desmethylvenlafaxine (ODV) was also unaffected. 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-hydroxydesipraine was reduced and desiramine AUC and C_{max} were increased by approximately 35%. Imipramine partially inhibited the formation of ODV but the total concentration of venlafaxine and its active metabolite remained unaffected and no dosage adjustment of venlafaxine is required.

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.

Risperidone: Venlafaxine increased the risperidone AUC by 32% but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

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 Efexor.

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 Efexor 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.

Venlafaxine is a relatively weak inhibitor of CYP2D6 and does not inhibit CYP1A2, CYP2C9 or CYP3A4. Therefore, Efexor is not expected to interact with other drugs metabolised by these hepatic enzymes.

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 Efexor XL is coadministered 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 Efexor XL is administered with cimetidine.

Antihypertensives: There is no evidence suggesting incompatibility between treatment with Efexor and treatment with either antihypertensives (including β-blockers, ACE inhibitors and diuretics) or hypoglycaemic agents.

Plasma protein binding: Venlafaxine and ODV are 27% and 30% bound to plasma proteins respectively. Drug interactions due to protein binding of venlafaxine and ODV are therefore not expected.

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

The safety of Efexor for use during human pregnancy has not been established. Therefore, the use of Efexor during known or suspected pregnancy is contra-indicated. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Insufficient data are available to support the use of Efexor in lactating women. Therefore, such use is contra-indicated.

4.7 Effects on ability to drive and use machines

Although Efexor 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 and therefore patients should be cautioned about their ability to drive a car or operate hazardous machinery.

4.8 Undesirable effects

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

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

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

Adverse events observed with venlafaxine, bot spontaneous and clinical trials reportings, 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):

Blood and lymphatic system disorders – **Uncommon**: ecchymosis, mucous membrane bleeding; **Rare**: prolonged bleeding time, haemorrhage, thrombocytopenia.

Cardiovascular and vascular disorders *(see Special warnings and special precautions for use)* – **Common**: hypertension, palpitation, vasodilatation;

Uncommon: postural hypotension, syncope, arrhythmias (including tachycardia).

Gastrointestinal disorders – **Very common**: constipation, nausea (see below); **Common**: anorexia, diarrhoea, dyspepsia, vomiting; **Uncommon**: bruxism.

General disorders – **Very common**: asthenia, headache; **Common**: abdominal pain, abnormal dreams, chills, pyrexia; **Rare**: anaphylaxis

Metabolic and nutritional disorders – **Common**: changes in serum cholestrol (see below); weight gain or loss; **Uncommon**: hyponatraemia including SIADH *(see Special warnings and special precautions for use),* increased liver enzymes (see below); **Rare**: hepatitis.

Musculo-skeletal disorders – **Common**: arthralgia, myalgia; **Uncommon**: muscle spasm.

Neurological disorders – **Very common**: dizziness, dry mouth, insomnia, nervousness, somnolence; **Common**: agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; **Uncommon**: hallucinations, myoclonus; **Rare**: disorders of balance and coordination, dyskinesia, dystonia, mania or hypomania (see Special warnings and special precautions for use), neuroleptic malignant syndrome-like effects, seizures (see Special Warnings and special precautions for use), serotonergic syndrome.

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.

Skin and subcutaneous tissue disorders – **Very common**: sweating; **Common**: pruritis, rash; **Uncommon**: angioedema, maculopapular eruptions, urticaria, photosensitivity reactions; **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:

Allergic reactions including urticaria or maculopapular eruptions accompanied by pruritus or angioedema generally resolve rapidly after drug discontinuation.

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

Serum cholesterol may be increased particularly with prolonged administration and possibly with higher doses. In placebo-controlled clinical trials, an increase in serum cholesterol from baseline, of / 1.3mmol/L (50mg/dL) and to a value of /6.7mmol/L (260mg/dL), was observed in 3% of venlafaxine-treated patients compared with 2% of placebo-treated patients.

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, paraesthesia, sweating and vertigo. The majority of symptoms experienced on withdrawal of Efexor are non-serious and self-limiting *(see also Posology and Administration).*

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 associated with overdosage ov venlafaxine, usually when in combination with alcohol and/or other CNS drugs.

Management of Overdosage – Ensure an adequate airway, oxygenation and ventilation. Monitoring of cardiac rhythm and vital signs is recommended as are general supportive and symptomatic measures. Use of activated charcoal, induction of emesis or gastric lavage should be considered. No specific antidotes for Efexor 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

Efexor 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 Efexor'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-desmethyl venlafaxine 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

The oral LD_{50} of venlafaxine in mice was 405mg/kg in female rats and 673mg/kg in male rats. These values are equivalent to 45-90 times the maximum recommended human dose.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Sodium starch glycolate
Magnesium stearate
Yellow iron oxide (E172)
Brown iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Blister packs containing 60 tablets in an outer cardboard carton

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
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8 Parallel Product Authorisation Number

PPA 0465/085/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First date of authorisation: 02 February 2002

Last date of authorisation: 02 February 2007

10 DATE OF REVISION OF THE TEXT

February 2009