PROFESSIONAL INFORMATION

ILLOVEX XR RANGE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ILLOVEX XR 37,5 mg extended release film coated tablets

ILLOVEX XR 75 mg extended release film coated tablets

ILLOVEX XR 150 mg extended release film coated tablets

ILLOVEX XR 225 mg extended release film coated tablets

ILLOVEX XR 300 mg extended release film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ILLOVEX XR 37,5 mg: Each extended release film coated tablet contains venlafaxine hydrochloride equivalent to 37,5 mg venlafaxine.

Contains sugar (lactose monohydrate 3,2 mg and mannitol 5 mg) per tablet.

ILLOVEX XR 75 mg: Each extended release film coated tablet contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Contains sugar (lactose monohydrate 3,6 mg and mannitol 10 mg) per tablet.

ILLOVEX XR 150 mg: Each extended release film coated tablet contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine.

Contains sugar (lactose monohydrate 6,0 mg and mannitol 20 mg) per tablet.

ILLOVEX XR 225 mg: Each extended release film coated tablet contains venlafaxine hydrochloride equivalent to 225 mg venlafaxine.

Contains sugar (lactose monohydrate 6,8 mg and mannitol 30 mg) per tablet.

ILLOVEX XR 300 mg: Each extended release film coated tablet contains venlafaxine hydrochloride equivalent to 300 mg venlafaxine.

Contains sugar (lactose monohydrate 9,2 mg and mannitol 40 mg) per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

ILLOVEX XR 37,5 mg: Round, biconvex, white, extended release film coated tablets, with a core diameter of 7 mm and core thickness of 4,2 mm.

ILLOVEX XR 75 mg: Round, biconvex, white, extended release film coated tablets, with a core diameter of 7,5 mm and core thickness of 4,2 mm.

ILLOVEX XR 150 mg: Round, biconvex, white, extended release film coated tablets, with a core diameter of 9,5 mm and core thickness of 5,1 mm.

ILLOVEX XR 225 mg: Round, biconvex, white, extended release film coated tablets, with a core diameter of 11 mm and core thickness of 6,2 mm.

ILLOVEX XR 300 mg: Round, biconvex, white, extended release film coated tablets, with a core diameter of 12,5 mm and a core thickness of 6,1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- ILLOVEX XR is indicated for the treatment of depression, including depression with associated anxiety.
- ILLOVEX XR is indicated for the prevention of relapses of an episode of depression in patients responding to an initial 6 to 8 weeks treatment. In patients responding to 6 months of relapse prevention, ILLOVEX XR may be used to prevent recurrence. Safety and efficacy beyond one year of therapy have not been demonstrated. When ILLOVEX XR is used for long-term it should periodically be re-evaluated for the usefulness of the product in the individual patient.
- ILLOVEX XR is indicated for the treatment of generalised anxiety disorder and for the treatment of Social Anxiety Disorder. The effectiveness of ILLOVEX XR in the treatment of Social Anxiety Disorder for more than 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Posology

The recommended dose for ILLOVEX XR is 75 mg (given as either 1 x 75 mg tablet or 2 x 37,5 mg tablets), once daily. If further clinical improvement is required after several weeks, the dose may be increased to 150 mg, taken once daily. The dose can be increased up to 225 mg once daily, if necessary.

Dosage increases should be made at intervals of 2 weeks or more, however, no less than 4 days apart. For depressed patients, the dose may be increased further, if needed, up to 375 mg, taken once daily.

ILLOVEX XR should be taken with food, at approximately the same time each day, either in the morning or evening.

Special populations

Impaired renal function:

Lower doses of ILLOVEX XR should be administered to patients with impaired renal function.

For patients with renal impairment with a glomerular filtration rate (GFR) of 10 – 70 mL/min, the total daily dose of ILLOVEX XR should be reduced by 25 – 50 %.

In haemodialysis patients, the total daily dose of ILLOVEX XR should be reduced by 50 %.

Individualisation of dosage may be required due to individual variability in these patients (see section 4.4).

Impaired hepatic function:

In patients with mild to moderate hepatic impairment, the total daily dose of ILLOVEX XR should be reduced by 50 %.

Patients with severe hepatic impairment have not been studied; therefore, caution should be used if considering treating these patients with ILLOVEX XR, and a further reduction should be considered.

Individualisation of dosage, including further dose reductions (> 50 %), may be required due to individual

variability in clearance among these patients (see section 4.4).

Elderly patients:

No specific dosage adjustments of ILLOVEX XR are recommended based on the patient's age.

Maintenance, continuation and extension of treatment:

The necessity for long-term treatment with ILLOVEX XR must be regularly reassessed. It is not known whether the dose of antidepressant required to induce remission, is identical to the dose needed to sustain and/or maintain euthymia.

Discontinuation of ILLOVEX XR:

When discontinuing treatment with ILLOVEX XR, dose tapering is recommended whenever possible (see section 4.4). If ILLOVEX XR has been taken for more than 6 weeks, it is recommended the dose be tapered over at least a two-week period.

Dose, duration of treatment and the individual patient may affect the period required for tapering of ILLOVEX XR.

Before abruptly discontinuing ILLOVEX XR, patients are advised to consult their doctor (see section 4.4).

Paediatric population

Children and adolescents up to 18 years:

ILLOVEX XR is contraindicated in children (see section 4.3.)

Method of administration

The tablets should be swallowed whole with fluid. Do not crush, divide, chew or dissolve tablet in water as the coating is intended to ensure prolonged release (see section 5.2).

4.3 Contraindications

- Hypersensitivity to venlafaxine or to any of the ingredients of ILLOVEX XR (see section 4.4)
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) (see section 4.5)

  Treatment with ILLOVEX XR must not be started for at least 14 days after discontinuation of treatment with an MAOI. Treatment with ILLOVEX XR must be stopped for at least 7 days before starting treatment with any MAOI (see section 4.5). Severe adverse reactions have been reported when the above dosing instructions were not followed. These reactions include diaphoresis, dizziness, flushing, hyperthermia with features resembling neuroleptic malignant syndrome, myoclonus, nausea, tremor, vomiting, seizures and death (see section 4.5)
- ILLOVEX XR should not be given to patients with uncontrolled hypertension
- Patients with a high risk of serious ventricular dysrhythmia should not take ILLOVEX XR
- Treatment with ILLOVEX XR is not recommended for patients with unstable epilepsy (see section 4.4)
- Children under the age of 18 years of age (see section 4.4)
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Suicidal thoughts or clinical worsening:

Patients treated with ILLOVEX XR should be monitored and observed closely for signs of clinical worsening and suicidality. Patients, families and caregivers should be alert for emergent signs of agitation, aggressiveness, akathisia (psychomotor restlessness), anxiety, hostility, hypomania, impulsivity, insomnia, irritability, mania, panic attacks, other unusual changes in behaviour, worsening of depression and suicidal thoughts, especially when starting therapy or when any changes are made to the dose or dosing schedule. The risk of attempted suicide must be considered, especially in depressed patients, and the lowest treatment dose should be provided in these circumstances, to reduce the risk of overdose.

Suicide is a known risk of certain psychiatric disorders, including depression, with the disorders themselves being strong predictors of suicide. Studies showed that antidepressant medicines (SSRIs and others) increase the risk of suicidality in children, adolescents and young adults (ages 18 – 24 years) with major depression and other psychiatric disorders.

Serotonin syndrome:

Serotonin syndrome, a potentially life-threatening condition, may occur with ILLOVEX XR treatment, especially when taken with other medicines which may affect the serotonergic neurotransmitter system.

Ocular effect:

Mydriasis may occur in patients treated with ILLOVEX XR. Patients with raised intra-ocular pressure or those at risk for acute narrow-angle glaucoma (angle closure glaucoma) should be closely monitored.

Major depressive disorder:

Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicine. The risk may persist until significant remission occurs. A casual role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with ILLOVEX XR should nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

Due to the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The subsequent symptoms have been reported in patients being treated with antidepressants for major

depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania and mania).

Although no causal link between the emergence of suicidal impulses has been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing ILLOVEX XR in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms. If the decision is made to discontinue treatment, ILLOVEX XR should be tapered (see section 4.2).

Cardiovascular disease:

ILLOVEX XR should not be used in patients with an identified very high risk of serious ventricular dysrhythmia or uncontrolled hypertension.

As ILLOVEX XR has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease, caution is advised due to the risk of dose-related increases in blood pressure and regular blood pressure monitoring is advised. Cases of elevated blood pressure requiring immediate treatment have been reported. Regular blood pressure monitoring is recommended for patients receiving ILLOVEX XR. Pre-existing hypertension should be controlled before treatment with ILLOVEX XR. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

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.

Epilepsy, seizures and convulsions:

Convulsions may occur with ILLOVEX XR therapy. ILLOVEX XR should be introduced with care in patients with a history of convulsions or epilepsy.

ILLOVEX XR should be avoided in patients with unstable epilepsy disease. Use of ILLOVEX XR should be

stopped in patients developing seizures or when there is an increase in seizure frequency.

Mania / hypomania:

ILLOVEX XR should be used cautiously in patients with a history or family history of bipolar disorder since mania/hypomania may occur in a small proportion of patients treated with mood disorders who are given ILLOVEX XR.

Aggression:

ILLOVEX XR should be used cautiously in patients with a history of aggression as aggression may occur in a small proportion of patients who have received ILLOVEX XR therapy, dose reduction or discontinuation.

Hyponatremia:

In volume-depleted or dehydrated patients taking ILLOVEX XR cases of hyponatremia and/or Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur. Patients taking diuretics, elderly patients and patients who are volume depleted may be at greater risk for these events.

Abnormal bleeding:

Medicines that inhibit serotonin uptake may cause abnormalities in platelet aggregation. ILLOVEX XR should be used cautiously in patients pre-disposed to bleeding, including patients on anti-coagulants and platelet inhibitors, since the risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased.

ILLOVEX XR may be associated with an increased risk of blood loss during surgery.

Postpartum haemorrhage

SNRIs, such as ILLOVEX XR, may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8).

Skin rash:

Patients should be advised to notify their doctor if they develop urticaria, a rash or a related allergic reaction (see section 4.3).

Weight loss medicine:

ILLOVEX XR in combination with weight loss medicine, including phentermine, has not been studied in terms of safety and efficacy. Therefore, co-administration of these products is not recommended. ILLOVEX XR is not indicated for weight loss, either alone or in combination with other medicines.

Serum cholesterol:

Measurement of serum cholesterol levels is recommended during the long-term therapy of ILLOVEX XR since increases of serum cholesterol have been observed in some patients.

Renal and Hepatic impairment:

ILLOVEX XR should be used with caution in patients with renal impairment, moderate to severe hepatic impairment or cirrhosis of the liver. Dosage adjustment may be necessary (see section 4.2).

Discontinuation of treatment:

Discontinuation effects are well known to occur. Therefore, discontinuation of ILLOVEX XR should be tapered gradually and the patient monitored (see section 4.2). Side effects may include hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleeping disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsions, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and vomiting. Studies indicate that the majority of discontinuation side effects are mild and resolve without treatment.

Use in elderly patients:

ILLOVEX XR appears to pose no exceptional safety problems for healthy elderly patients.

Abuse and dependence:

Studies did not reveal any evidence of drug-seeking behaviour, development of tolerance, or dose escalation over time.

Akathisia/psychomotor restlessness

The use of venlafaxine, as in ILLOVEX XR, has been related to 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 damaging.

Dry mouth

In 10 % of patients treated with venlafaxine, as in ILLOVEX XR, dry mouth was reported. The risk of caries is thus increased, and patients should be advised about the importance of dental hygiene.

Diabetes

In patients with diabetes, treatment with an SSRI or venlafaxine (as in ILLOVEX XR) may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine (as contained in ILLOVEX XR). This is due to non-specificity of the screening tests. False positive test results can be expected for several days following the termination of venlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will differentiate

venlafaxine from PCP and amphetamine.

Paediatric population

Children and adolescents up to 18 years:

The safety and efficacy of ILLOVEX XR in children under 18 years of age has not been established. Studies indicate an increase of hostility and suicide-related side effects such as suicidal ideation and self-harm (see section 4.3).

ILLOVEX XR contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosemia, total lactase deficiency or glucose-galactose malabsorption should not take ILLOVEX XR. ILLOVEX XR contains mannitol, which may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors

Patients who have recently discontinued MAOI therapy and started taking ILLOVEX XR, or those who have recently stopped ILLOVEX XR treatment before the initiation of MAOI therapy, have reported severe adverse reactions. These reactions include diaphoresis, dizziness, flushing, hyperthermia with features resembling neuroleptic malignant syndrome, myoclonus, nausea, tremor, vomiting, seizures and death (see section 4.3).

CNS active medicines

Caution is advised when ILLOVEX XR is taken with other CNS-active medicines, since the risk of this concomitant treatment has not been evaluated.

Medicines which may affect serotonergic neurotransmitter system:

Serotonin syndrome, a potentially life-threatening condition, may occur with ILLOVEX XR treatment,

especially when taken with other medicines which may affect the serotonergic neurotransmitter system (including lithium, sibutramine, SSRIs, other SRNIs, tramadol, triptans, or St. John's Wort (*Hypericum perforatum*), medicines which impair the metabolism of serotonin (i.e. MAOIs; including linezolid [a reversible non-selective MAOI antibiotic] (see section 4.3), or with serotonin precursors (such as tryptophan supplements). In addition, serotonin syndrome associated with the use of SNRI's with serotonin (5-HT_1) agonists such as sumatriptan has also been reported.

The symptoms of serotonin syndrome include autonomic instability, mental status changes, gastrointestinal symptoms and/or neuromuscular aberrations (see section 4.3).

If ILLOVEX XR is taken concomitantly with another SNRI, a SSRI or triptan (a 5-hydroxytriptamine receptor antagonist), it is advisable to carefully observe the patient, especially at the start of treatment or when a dose in increased. The concomitant use of ILLOVEX XR with serotonin precursors (such as tryptophan) is not recommended (see section 4.4).

Metoclopramide

Signs associated with serotonin syndrome have occurred after co-administration of venlafaxine (as contained in ILLOVEX XR) and intravenous administration of metoclopramide. These signs included agitation, confusion, diaphoresis, dilated pupils, facial twitching, generalised shaking, horizontal nystagmus and myoclonus.

Antidysrhythmics

ILLOVEX XR, when taken concomitantly with antidysrhythmic medicine, (e.g. propafenone), may lead to psychosis with raised serum concentrations of venlafaxine (as contained in ILLOVEX XR), which improve when treatment is discontinued.

Antibacterials

Severe abdominal cramps, cold sweats, profuse diarrhoea, tingling in the tip of the tongue, intense paraesthesia in the fingers, uncontrolled shivering and tremor may occur in patients taking ILLOVEX XR with antibacterial medicine, co-amoxiclav.

Antipsychotics

Neuroleptic malignant syndrome may develop in patients taking ILLOVEX XR with antipsychotics (e.g. chlorpromazine).

Indinavir

When taken concomitantly with ILLOVEX XR, the AUC of indinavir decreased by 28 % and it's C_{max} decreased by 36 %. The pharmacokinetics of venlafaxine (as contained in ILLOVEX XR) and its major metabolite O-desmethylvenlafaxine were unchanged. The clinical significance of this interaction is not known.

Anticoagulants

Venlafaxine (as in ILLOVEX XR) has been associated with bleeding disorders and other effects on the blood, occasionally. It is advised to give ILLOVEX XR with caution in combination with other medicine known to affect platelet function.

Ethanol

Although ILLOVEX XR does not increase the impairment of motor or mechanical skills caused by ethanol, it is advisable for patients to avoid consuming alcohol whilst taking ILLOVEX XR.

Haloperidol

When taken concomitantly with venlafaxine (as contained in ILLOVEX XR), the total oral clearance of

haloperidol decreased by 42 %, AUC increased by 70 %, C_{max} increased by 88 % but no change in half-life. In patients treated with both haloperidol and ILLOVEX XR, this should be taken into account.

Cimetidine

Cimetidine, at steady-state, inhibits first-pass metabolism of venlafaxine (as contained in ILLOVEX XR), resulting in a decrease in clearance of 43 % and an increase in maximum plasma concentrations of around 60 %. There is no apparent effect on the pharmacokinetics of its major metabolite O-desmethylvenlafaxine. The overall pharmaceutical activity of venlafaxine plus O-desmethylvenlafaxine is expected to increase only slightly in most patients. However, this may be more pronounced in elderly patients or in those with hepatic or renal impairment, or pre-existing hypertension.

Imipramine

Although venlafaxine (as contained in ILLOVEX XR) does not affect the pharmacokinetics of imipramine and 2-OH-imipramine, the AUC, C_{max} and C_{min} of desipramine increases by about 35 % in the presence of venlafaxine. The AUC of 2-OH-desipramine increases 2,5 to 4,5-fold. Imipramine does not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. In patients treated with both imipramine and ILLOVEX XR, this should be taken into account.

Ketoconazole

In extensive and poor metabolisers of CYP2D6, a higher plasma concentration of both venlafaxine (as contained in ILLOVEX XR) and its major metabolite O-desmethylvenlafaxine was observed in subjects following administration of ketoconazole.

Metoprolol

An increase in the plasma concentration of metoprolol by approximately 30 – 40 %, without altering the plasma concentration of its active metabolite α-hydroxymetoprolol, was observed when venlafaxine (as

contained in ILLOVEX XR) was administered concomitantly. Another study showed that the blood pressure lowering effects of metoprolol are reduced when taking ILLOVEX XR; although the significance of this clinical finding in hypertensive patients is not known.

Metoprolol does not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. Caution should be observed when treating patients with both metoprolol and ILLOVEX XR.

Risperidone

Venlafaxine (as contained in ILLOVEX XR) increases the AUC of risperidone by 32 %, however does not significantly change the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone). The significance of this clinical interaction is not known.

Diazepam

Diazepam does not appear to affect the pharmacokinetics of either venlafaxine (as contained in ILLOVEX XR) or O-desmethylvenlafaxine. ILLOVEX XR has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite desmethyldiazepam.

Lithium

Concomitant treatment of ILLOVEX XR and lithium does not affect the steady-state pharmacokinetics of venlafaxine (as contained in ILLOVEX XR). ILLOVEX XR, also, has no effects on the pharmacokinetics of lithium.

Medicines highly bound to plasma proteins

Venlafaxine (as contained in ILLOVEX XR) is only 27 % bound to plasma proteins, therefore co-administration of ILLOVEX XR with other medicines which are highly bound to plasma proteins is not expected to cause increased free concentrations of these other medicines.

Medicines metabolised by cytochrome P450 isoenzymes

ILLOVEX XR is a relatively weak inhibitor of CYP2D6 and does not inhibit CYP3A4 (e.g. alprazolam, carbamazepine), CYP1A2 (e.g. caffeine), CYP3A4 and CYP21C19 (e.g. diazepam) and CYP2C9 (e.g. tolbutamide).

Potential for other medicines to affect ILLOVEX XR

The metabolic pathways for ILLOVEX XR include CYP2D6 and CYP3A4. ILLOVEX XR is primarily metabolised to its active metabolite O-desmethylvenlafaxine by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of ILLOVEX XR.

CYP2D6 inhibitors

The metabolism of venlafaxine (as contained in ILLOVEX XR) to O-desmethylvenlafaxine may be decreased by concomitant use of CYP2D6 inhibitors. The resulting increased plasma concentration of venlafaxine and decreased concentration of O-desmethylvenlafaxine require no dosage adjustment since both are pharmacologically active.

CYP3A4 inhibitors

CYP3A4 inhibitors, when taken concomitantly with ILLOVEX XR, may increase levels of ILLOVEX XR and O-desmethylvenlafaxine. Therefore, caution is advised when treating patients with both ILLOVEX XR and a CYP3A4 inhibitor.

CYP2D6 and 3A4 inhibitors:

The use of ILLOVEX XR with CYP2D6 and CYP3A4 inhibitors (the primary metabolising enzymes for ILLOVEX XR) has not been studied. However, this combined treatment would be expected to increase the plasma concentration of ILLOVEX XR. Caution is therefore advised when combining ILLOVEX XR with medicines which produce simultaneous inhibition of these two enzyme systems.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see 4.3).

Pregnancy

ILLOVEX XR must not be administered to pregnant women.

Complications requiring tube-feeding, respiratory support or prolonged hospitalisation developed late in the third trimester in some neonates exposed to ILLOVEX XR. Such complications can occur immediately upon delivery.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breastfeeding

ILLOVEX XR must not be administered to lactating women.

ILLOVEX XR and its metabolite O-desmethylvenlafaxine are excreted in human milk, therefore mothers on treatment with ILLOVEX XR should not breastfeed.

Patients should be advised to notify their doctor, pharmacist or other healthcare professional should they become pregnant or intend to become pregnant whilst taking ILLOVEX XR.

Fertility

Reduced fertility was observed in a study in which both male and female rats were exposed to O-desmethylvenlafaxine. The human relevance of this finding is unknown.

4.7 Effects on ability to drive and use machines:

ILLOVEX XR may affect a patient's judgement, their ability to think and their motor skills. Patients should

therefore be cautioned about their ability to drive and operate machinery whilst taking ILLOVEX XR. Patients (especially the elderly) should be warned of the risk of dizziness and unsteadiness due to orthostatic hypotension.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed side effects associated with the use of ILLOVEX XR are nervous system related. The occurrence of side effects frequently observed are dose related.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Ecchymosis, haemorrhage including gastrointestinal bleeding
	Frequency unknown	Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia, blood dyscrasias (including agranulocytosis, aplastic anaemia, neutropenia, pancytopenia),
Metabolism and nutrition disorders	Frequent	Increased serum cholesterol (particularly with prolonged administration and possibly with higher doses), weight loss, decreased appetite
	Less frequent	Altered taste, hyponatremia, weight gain
Endocrine disorders	Frequency unknown	Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion, increased prolactin

Psychiatric disorders	Frequent	Abnormal dreams, nervousness, insomnia, decreased libido, anxiety, agitation, depersonalisation
	Less frequent	Apathy, hallucinations, manic reaction, activation of mania or hypomania, derealisation
	Frequency unknown	Delirium, abnormal thinking, aggression, amnesia, depression, emotional lability, suicidal ideation and behaviours
Nervous system disorders	Frequent	Dizziness, hypertonia, paraesthesia, tremor, headache, somnolence, sedation, akathisia, dysgeusia
	Less frequent	Myoclonus, convulsion, dysarthria, syncope, balance disorder, abnormal co-ordination
	Frequency unknown	Neuroleptic Malignant Syndrome (NMS), serotonin syndrome, tardive dyskinesia, hypoaesthesia, trismus
Eye disorders	Frequent	Abnormality of accommodation, mydriasis, visual disturbances
	Frequency unknown	Angle closure glaucoma

Ear and labyrinth disorders	Frequent	Tinnitus
	Frequency unknown	Vertigo
Cardiac disorders	Frequent	Palpitations, tachycardia
	Less frequent	Dysrhythmias, electrocardiogram QT prolongation, ventricular fibrillation, ventricular tachycardia (including *torsade de pointes*)
Vascular disorders	Frequent	Hypertension, vasodilation (hot flushes/flashes), dose related increases in blood pressure
	Less frequent	Orthostatic or postural hypotension, syncope
	Frequency unknown	Hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, yawning
	Less frequent	Interstitial lung disease, pulmonary eosinophilia
	Frequency unknown	Pharyngitis, rhinitis

Gastrointestinal disorders	Frequent	Decreased appetite, constipation, nausea, vomiting, anorexia, diarrhoea, dyspepsia, abdominal pain, dry mouth
	Less frequent	Bruxism, pancreatitis, gastrointestinal haemorrhage (see blood and lymphatic disorders)
	Frequency unknown	Increased appetite, eructation, flatulence
Hepatobiliary disorders	Less frequent	Reversible increases in liver enzymes, hepatitis
	Frequency unknown	Abnormal liver function test
Skin and subcutaneous tissue disorders	Frequent	Sweating, pruritus, hyperhidrosis (including night sweats), rash
	Less frequent	Angioedema, alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, photosensitivity reaction (see general disorders and administrative site conditions), toxic epidermal necrolysis, ecchymosis (see blood and lymphatic system disorders)
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, hypertonia, paraesthesia, myalgia
	Less frequent	Ataxia, muscle spasm, rhabdomyolysis

Renal and urinary disorders	Frequent	Urinary hesitation, urinary frequency, pollakiuria
	Less frequent	Urinary retention, urinary incontinence
Reproductive system and breast disorders	Frequent	Abnormal ejaculation/orgasms (male), anorgasmia, erectile dysfunction, sexual dysfunction
	Less frequent	Abnormal orgasm (female), galactorrhoea, menstrual changes, menorrhagia
	Frequency unknown	Menstrual disorders associated with increased bleeding or increased irregular bleeding (e.g. menorrhagia, metrorrhagia), post partum haemorrhage
General disorders and administrative site conditions	Frequent	Asthenia/fatigue, headache, pain, abdominal pain, back pain, chest pain, chills, fever
	Frequency unknown	Photosensitivity reactions, anaphylaxis, mucosal haemorrhage, angioedema
Investigations	Frequent	Increased blood cholesterol

c. Description of selected adverse reactions

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

d. Paediatric population

Children and adolescents up to 18 years:

The side effects profile of ILLOVEX XR in children and adolescents is similar to that as observed in adults, however, increased reports of hostility and, especially in children and adolescents with Major Depressive Disorder, suicide-related side effects such as suicidal ideation and self-harm have been reported. As with adults, decreased appetite, weight loss, increased blood pressure and increased serum cholesterol have been observed. Abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis and myalgia, in particular, have been observed (see section 4.3 and 4.4).

Discontinuation of treatment

Discontinuation of ILLOVEX XR (particularly when abrupt) commonly leads to withdrawal symptoms. Fatigue, somnolence, anorexia, palpitations, dizziness, dry mouth, diarrhoea, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nervousness, confusion, hypomania, nausea and/or vomiting, tremor, vertigo, 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 ILLOVEX XR treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.4 and section 4.2)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose of ILLOVEX XR, mainly in combination with alcohol and/or other medicines, has been reported.

Signs and symptoms:

The most common adverse effects of overdose include changes in the level of consciousness (ranging from somnolence to coma), convulsions, mydriasis, tachycardia and vomiting. Other adverse effects include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo and death.

ILLOVEX XR overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant medicines, but lower than that for tricyclic antidepressants. Indications are that ILLOVEX XR treated patients have a higher burden of suicide risk factors than SSRI-treated patients.

The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of ILLOVEX XR in overdosage, as opposed to some characteristics of venlafaxine-treated (as contained in ILLOVEX XR) patients, is not clear. Prescriptions for ILLOVEX XR should be written for the smallest quantity of the medicine, 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.

The administration of activated charcoal may also limit the absorption of ILLOVEX XR.

No specific antidotes are known for ILLOVEX XR, and forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC code: NO6A X16

Pharmacological classification: A.1.2 Psychoanaleptics (antidepressants)

Venlafaxine and its major metabolite, O-desmethylvenlafaxine, are inhibitors of norepinephrine (noradrenaline) and serotonin re-uptake and also weakly inhibit the re-uptake of dopamine.

Venlafaxine and O-desmethylvenlafaxine reduce beta-adrenergic responsiveness after both single dose (acute) and chronic administration.

Venlafaxine and O-desmethylvenlafaxine appear to have equal potencies with respect to their overall action on receptor binding and neurotransmitter re-uptake.

Venlafaxine does not possess Monoamine Oxidase (MAO) inhibitory activity.

5.2 Pharmacokinetic properties

Absorption:

Venlafaxine undergoes extensive first pass metabolism and is well absorbed. The bioavailability of venlafaxine is 10 – 45 %.

Peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 6,0 $\pm$ 1,5 and 8,8 $\pm$ 2,2 hours respectively, after administration.

The AUC (extent of absorption) is the same as the venlafaxine immediate release tablet, and fluctuations in plasma concentrations are slightly lower following treatment with a slow release tablet than an immediate release tablet.

Distribution:

The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours,

respectively. Plasma concentrations of venlafaxine and O-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and O-desmethylvenlafaxine are less than 35 % bound to plasma proteins (Venlafaxine and O-desmethylvenlafaxine are 27 % and 30 %, respectively, bound to plasma proteins).

Biotransformation:

Venlafaxine is metabolised extensively in the liver, and the major metabolite of venlafaxine is O-desmethylvenlafaxine.

Elimination:

Excretion of venlafaxine and its metabolites is mainly through the kidneys. The recovery of a venlafaxine dose is approximately 87 % in the urine within 48 hours, as either unchanged venlafaxine, unconjugated O-desmethylvenlafaxine, or other minor metabolites.

Linearity/non-linearity:

Venlafaxine and O-desmethylvenlafaxine exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Effects of food:

The extent of absorption of venlafaxine or the subsequent formation of O-desmethylvenlafaxine are not affected when venlafaxine is administered with food.

Pharmacokinetics in special patient groups

Elderly patients:

In subjects over 60 years of age, a 20 % reduction in clearance of O-desmethylvenlafaxine was noted, although this does not warrant dose adjustment in this population.

Patients with renal impairment:

The total clearance of both venlafaxine and O-desmethylvenlafaxine was reduced and $t_{1/2}$ was prolonged in patients with moderate to severe renal impairment.

In subjects with creatinine clearance <30 mL/min, the reductions in total clearance were most pronounced. Dosage adjustment is recommended in these patients (see section 4.2).

Patients with hepatic impairment:

In patients with mild to moderate hepatic impairment (compensated hepatic cirrhosis), the pharmacokinetics of both venlafaxine and O-desmethylvenlafaxine were significantly altered. Significantly higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine were present as a result of the reduction in both the metabolism of venlafaxine and elimination of O-desmethylvenlafaxine. Dosage adjustment is recommended in these patients (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Silica colloidal anhydrous

Coating

Cellulose acetate

Macrogol

Hypromellose E464

Lactose monohydrate

Titanium dioxide E171

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

30’s pack: Each cardboard carton encloses 3 x transparent PVC-PCTFE/Aluminium blisters strips containing 10 tablets each.

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

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

ILLOVEX XR 37,5 mg: A 48/1.2/0910

ILLOVEX XR 75 mg: A 48/1.2/0911

ILLOVEX XR 150 mg: A 48/1.2/0912

ILLOVEX XR 225 mg: A 48/1.2/0913

ILLOVEX XR 300 mg: A53/1.2/0467

9. DATE OF FIRST AUTHORISATION

Date of registration

ILLOVEX XR 37,5 - 225 mg: 22 June 2021

ILLOVEX XR 300 mg: 16 July 2021

10. DATE OF REVISION OF THE TEXT

3 September 2021