APPROVED PROFESSIONAL INFORMATION FOR EXLOV RANGE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

EXLOV XR 50 mg extended release tablets

EXLOV XR 100 mg extended release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXLOV XR 50 mg: Each extended release tablet contains desvenlafaxine benzoate equivalent to 50 mg desvenlafaxine.

EXLOV XR 100 mg: Each extended release tablet contains desvenlafaxine benzoate equivalent to 100 mg desvenlafaxine.

EXLOV XR tablets are sugar free.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

EXLOV XR 50 mg: Light pink, biconvex, round shaped extended release film coated tablets debossed with "DV" on one side and "50"on the other side.

EXLOV XR 100 mg: Reddish-orange, biconvex, round shaped extended release film coated tablets, debossed with "DV" on one side and "100"on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXLOV XR tablets are indicated for the treatment of major depressive disorder (MDD).

4.2 Posology and method of administration

The recommended dose for EXLOV XR is 50 mg once daily, with or without food, with a maximum dose of 100 mg per day.

The dose increase should occur gradually and at an interval of not less than 7 days.

Special populations

Use in patients with renal impairment

The recommended starting dose in patients with severe renal impairment (24-hr CrCl <30 ml/min) or end-stage renal disease (ESRD) is 50 mg every other day. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable. Supplemental doses should not be given to patients after dialysis (see section 5.2).

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric use

The safety and efficacy of EXLOV XR in patients less than 18 years of age have not been established.

Use in elderly patients

No dosage adjustment is required solely on the basis of age, however, possible reduced renal clearance of EXLOV XR should be considered when determining dose (see section 5.2).

Method of administration

The route of administration is oral. Tablets are to be taken once a day with or without food.

Discontinuation of EXLOV XR

Symptoms associated with the discontinuation of EXLOV XR, other SNRIs and SSRIs have been reported. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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 medical practitioner may continue decreasing the dose but at a more gradual rate (see section 4.4 and section 4.8).

Switching patients from other antidepressants to EXLOV XR

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to EXLOV XR.

Tapering of the initial antidepressant may be necessary to minimise discontinuation symptoms.

4.3 Contraindications

- hypersensitivity to desvenlafaxine, venlafaxine hydrochloride or to any excipients in the EXLOV XR formulation
- EXLOV XR is an inhibitor of both norepinephrine and serotonin reuptake. EXLOV XR must not be used in combination with a monoamine oxidase inhibitor (MAOI) including linezolid, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of EXLOV XR, at least 7 days should be allowed after stopping EXLOV XR before starting an MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines such as EXLOV XR soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of SSRI/SNRI medicines. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death (see section 4.5)
- children less than 18 years of age, as safety and efficacy have not been established (see sections 4.5 and 4.8)
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Clinical worsening of depressive symptoms, unusual changes in behaviour, and suicidality

Patients with major depressive disorder may experience worsening of their depression and/ or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant

remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with EXLOV 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.

Because of 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 disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following 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 a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing EXLOV XR in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, EXLOV XR should be tapered (see section 4.2).

Short-term trials did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults aged 65 years and older.

There have been reports of hostility, suicidal ideation and self-harm with use of SSRIs in children under the age of 18 years.

EXLOV XR should be used cautiously in patients with a history or family history of mania or hypomania (see section 4.8).

Serotonin syndrome

The development of a potentially life-threatening serotonin syndrome may occur with EXLOV XR treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs and triptans) and with medicines that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhoea) (see section 4.5).
The concomitant use of EXLOV XR with serotonin precursors (such as tryptophan supplements) is not recommended.
Treatment with EXLOV XR should be discontinued if serotonin syndrome or neuroleptic malignant syndrome (NMS)-Like reactions occur and supportive symptomatic treatment initiated.

Narrow-angle glaucoma

Mydriasis has been reported in association with EXLOV XR; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored (see section 4.8).

Ischaemic cardiac adverse events

Studies indicate less frequent reports of ischaemic cardiac adverse events, including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation in patients with multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine, as contained in EXLOV XR, treatment as compared to placebo.

Discontinuation symptoms

Adverse reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical trials at a rate of ≥ 2 % include: dizziness, withdrawal syndrome, nausea and headache. In general, discontinuation symptoms occurred more frequently with longer duration of therapy (see section 4.2).

Adverse reactions leading to discontinuation of therapy

The most common adverse reaction leading to discontinuation in at least 2 % of the desvenlafaxine treated patients in short-term studies (up to 12 weeks) was nausea (2 %) and in long-term studies (up to 11 months), no events lead to discontinuation in at least 2 % of the patients and at a rate greater than placebo in the double-blind phase.

Adverse reactions reported with other SNRIs

Although gastrointestinal bleeding is not considered an adverse reaction for EXLOV XR, it is an adverse reaction for other SNRIs and may also occur with EXLOV XR.

Effects on activities requiring concentration and performance

Interference with cognitive and motor performance

The results of a study that assessed the effects of desvenlafaxine, contained in EXLOV XR, on behavioural performance of healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behaviour performance. However, since any central nervous system (CNS) -active medicine may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that EXLOV XR therapy does not adversely affect their ability to engage in such activities.

Abuse and dependence

Physical and psychological dependence

Although desvenlafaxine has not been studied in preclinical or clinical trials for its potential for abuse, no indication of medicine-seeking behaviour was seen in those studies that have been conducted.

Co-administration of medicines containing venlafaxine and/or desvenlafaxine as contained in EXLOV XR

Desvenlafaxine is the major active metabolite of venlafaxine, a medicine used to treat major depressive, generalised anxiety, social anxiety and panic disorders.

EXLOV XR should not be used concomitantly with medicines containing venlafaxine hydrochloride or other medicines containing desvenlafaxine.

Effects on blood pressure

Increased blood pressure

Studies have shown increases in blood pressure in some patients, particularly with higher doses. Pre-existing hypertension should be controlled before treatment with EXLOV XR. Patients receiving EXLOV XR should have regular monitoring of blood pressure.

Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine.

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving EXLOV XR, either dose reduction or discontinuation should be considered.

Caution should be exercised in treating patients with underlying conditions that might be compromised by increases in blood pressure (see section 4.8).

Postural hypotension (see section 5.2).

Cardiovascular/cerebrovascular

Caution is advised in administering EXLOV XR to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders.

Increases in blood pressure and heart rate were observed in clinical trials with desvenlafaxine.

EXLOV XR has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for those with cerebrovascular disease, were excluded from studies conducted (see section 4.8).

Serum lipids

Dose-related elevations in fasting serum total cholesterol. LDL (low density lipoprotein) cholesterol, and triglycerides have been observed. Measurement of serum lipids should be considered during treatment with EXLOV XR (see section 4.8).

Seizures

Cases of seizure have been reported in studies with desvenlafaxine, as contained in EXLOV XR.

Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from studies conducted. EXLOV XR should be prescribed with caution in patients with a seizure disorder (see section 4.8).

Discontinuation effects

There have been spontaneous reports of adverse events occurring upon discontinuation of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors) such as EXLOV XR, particularly when discontinuation is abrupt. Reported adverse events include dysphoric mood,

irritability, agitation, dizziness, sensory disturbances (e.g. paraesthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Whilst these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored when discontinuing treatment with EXLOV XR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

If intolerable symptoms occur following a decrease in the dose, or upon discontinuation of treatment, resuming the previously prescribed dose may be considered (see sections 4.2 and 4.8).

Abnormal bleeding

Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation.

Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, haematoma, epistaxis, and petechiae to life-threatening haemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of desvenlafaxine and NSAIDs, aspirin, or other medicines that affect coagulation or bleeding.

As with other medicines that inhibit serotonin-reuptake, EXLOV XR should be used cautiously in patients predisposed to bleeding.

Hyponatraemia

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion have been described with SNRIs and SSRIs, including EXLOV XR, usually in volume-depleted or dehydrated patients, including the elderly and those patients taking diuretics (see section 4.8).

Sexual Dysfunction:

SNRIs may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs such as EXLOV XR.

Antidepressants and Post-partum Haemorrhage

Clinical studies have demonstrated an increased risk of post-partum haemorrhage (PPH) in mothers exposed to SNRI therapy in the last month of pregnancy. The adjusted odd-ratio (OR) for an increased risk of PPH in mothers exposed to a SNRI in the final month of pregnancy was 1,76 (95 % CI 1,47-2,11) compared to non-exposed mothers.

The risk of PPH was affected by type of antidepressant, mode of delivery and time of exposure.

For type of antidepressant, the most pronounced risk was found among SNRI users (Relative Risk [RR]=1,62; 95 % CI 1,41-1,85). A higher risk was found in exposed patients who underwent Caesarean sections (RR=2,02, 95 % CI 1,61-2,54) compared to vaginal delivery (RR=1,43, 95 % CI 1,15-1,78). There was no increase in risk of PPH associated with past use of antidepressants. However, there was a further increase in risk among recent SNRI users (RR=1,73, 95 % CI 1,5-2,0) and current SNRI users (RR = 1,79, 95 % CI 1,53-2,10).

Elderly

No dosage adjustment is required solely on the basis of age, however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see sections 4.2 and section 5.2). Although only 5 % of patients in studies of desvenlafaxine, as contained in EXLOV XR, were aged 65 or older, no overall differences in safety or efficacy were observed between the elderly and younger patients. However, in the short-term placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients treated with desvenlafaxine who were ≥ 65 years of age (8 %) compared to patients < 65 years of age (0,9 %). In addition, in both short-term and long-term placebo-controlled studies, there were increases in systolic blood pressure in patients ≥ 65 years of age compared to patients < 65 years of age treated with desvenlafaxine.

Laboratory test interactions:

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine (as contained in EXLOV XR). This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of EXLOV XR therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine.

Paediatric population

Safety and efficacy in children under 18 years of age have not been established (see sections 4.3 and 4.8). During studies of SSRIs and SNRIs in major depressive

disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm in this age group (see section 4.3 and section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to EXLOV XR (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Concomitant use of EXLOV XR in patients taking monoamine oxidase inhibitors (MAOIs) including linezolid is contraindicated (see sections 4.3 and section 4.4).

Central nervous system (CNS)-active medicines

The risk of using EXLOV XR in combination with other central nervous system (CNS) active medicines has not been systematically evaluated. Consequently, caution is advised when EXLOV XR is taken in combination with other CNS-active medicines.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with EXLOV XR treatment, particularly with concomitant use of other medicines that may

affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, St. John's Wort [*Hypericum perforatum*], pethidine), with medicines that impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], (see section 4.3), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms (see section 4.4).

Ethanol

Patients should be advised to avoid alcohol consumption while taking EXLOV XR.

Potential for other medicines to affect EXLOV XR

Inhibitors of CYP3A4

CYP3A4 is involved in desvenlafaxine elimination. Studies indicate that ketoconazole (200 mg twice daily) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine, as contained in EXLOV XR**,** (400 mg single dose) by approximately 43 %, a weak interaction and C_{max} by about 8 %. Concomitant use of **EXLOV XR** with potent inhibitors of CYP3A4 may result in higher exposure to desvenlafaxine.

Inhibitors of other CYP enzymes

Based on *in vitro* data, medicines that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine (as contained in EXLOV XR).

Potential for EXLOV XR to affect other medicines

Medicines metabolised by CYP2D6

Studies have shown that desvenlafaxine is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. When desvenlafaxine (as contained in EXLOV XR) was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased approximately 17 %. When 400 mg was administered, the AUC of desipramine increased approximately 90 %. When desvenlafaxine, as contained in EXLOV XR, was administered at a dose of 100 mg daily in conjunction with a single 60 mg dose of codeine, a CYP2D6 substrate metabolised to morphine, the AUC of codeine was unchanged, the AUC of morphine decreased approximately 8 %. Concomitant use of EXLOV XR with a medicine metabolised by CYP2D6 may result in increased concentrations of that medicine and decreased concentrations of its CYP2D6 metabolites.

Medicines metabolised by CYP3A4

In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozymes. Studies in which, desvenlafaxine (as contained in EXLOV XR) was administered (at a dose of 400mg daily) in conjunction with a single 4 mg dose of midazolam, a CYP3A4 substrate, the AUC of midazolam decreased by approximately 31 %. A second study in which desvenlafaxine 50 mg daily was co-administered with a single 4 mg dose of midazolam resulted in the AUC and C_{max} of midazolam having decreased by approximately 29 % and 14 % respectively. Concomitant use of EXLOV XR with a medicine metabolised by CYP3A4 may result in lower exposures to that medicine.

Medicines metabolised by a combination of both CYP2D6 and CYP3A4 (tamoxifen and aripiprazole)

Studies have proved that desvenlafaxine (as contained in EXLOV XR) 100 mg daily, has no clinically relevant effect on medicines metabolised by a combination of both CYP2D6 and CYP3A4 enzymes.

A single 40 mg dose of tamoxifen, which is metabolised to active metabolite 4-hydroxy-tamoxifen and endoxifen primarily by CYP2D6 with minor contributions to metabolism by CYP3A4, was administered in conjunction with desvenlafaxine (as contained in EXLOV XR) 100 mg daily. The AUC increased by 3 % with concomitant administration of desvenlafaxine (as contained in EXLOV XR) whilst the AUC of 4-hydroxy-tamoxifen was increased by 9 % and endoxifen AUC was decreased by 12 %.

Desvenlafaxine (as contained in EXLOV XR) was administered at a dose of 100 mg daily in conjunction with a single 5 mg dose of aripiprazole, a CYP2D6 and CYP3A4 substrate metabolised to the active metabolite dehydro-aripiprazole. The AUC of aripiprazole increased by 6 %, with concomitant administration of desvenlafaxine. The AUC of dehydro-aripiprazole increased by 3 %, with concomitant administration.

Medicines metabolised by CYP1A2, 2A6, 2C8, 2C9 and 2C19

In vitro, desvenlafaxine (as contained in EXLOV XR) does not inhibit CYP1A2, 2A6, 2C8, 2C9 and 2C19 isoenzymes and would not be expected to affect the pharmacokinetics of medicines that are metabolised by these CYP isoenzymes.

P-glycoprotein transporter

In vitro, desvenlafaxine (as contained in EXLOV XR) is not a substrate or an inhibitor for the P-glycoprotein transporter.

Electroconvulsive therapy

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with EXLOV XR treatment for major depressive disorder (MDD).

4.6 Fertility, pregnancy and lactation

EXLOV XR must not be administered to pregnant or lactating women. Safety during pregnancy and lactation have not been established (see section 4.3).
Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see section 4.4, 4.8).

Pregnancy

Studies have demonstrated that desvenlafaxine crosses the human placenta. If EXLOV XR is used until, or shortly before birth, discontinuation effects in the newborn may occur.
Complications, including the need for respiratory support, tube-feeding or prolonged hospitalisation, have been reported in neonates exposed to SNRIs or SSRIs late in the third trimester. Such complications can arise immediately upon delivery. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Lactation

EXLOV XR (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue **EXLOV XR**, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines:

EXLOV XR may impair judgement, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery whilst taking EXLOV XR.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequent Less frequent	Decreased appetite Hyponatraemia

Psychiatric disorders	Frequent Less frequent	Insomnia, anxiety, abnormal dreams, nervousness, decreased libido, anorgasmia, irritability Withdrawal syndrome, abnormal orgasm, depersonalisation, hypomania, hallucinations
Nervous system disorders	Frequent Less frequent	Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention Syncope, convulsion, dystonia, extrapyramidal disorder, dyskinesia, Serotonin syndrome
Eye disorders	Frequent	Blurred vision, mydriasis
Ear and labyrinth disorders	Frequent	Tinnitus, vertigo

Cardiac disorders	Frequent Less frequent	Palpitations, tachycardia Stress cardiomyopathy (Takotsubo cardiomyopathy)
Vascular disorders	Frequent Less frequent	Hot flush, increased blood pressure Orthostatic hypotension**, peripheral coldness
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Yawning Epistaxis
Gastrointestinal disorders	Frequent Less frequent	Nausea, dry mouth, constipation, diarrhoea, vomiting Pancreatitis acute
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency not known	Hyperhidrosis, rash Alopecia, photosensitivity reaction, angioedema Stevens-Johnson syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent	Musculoskeletal stiffness

Renal and urinary disorders	Less frequent	Urinary hesitation, proteinuria, urinary retention
Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Erectile dysfunction*, delayed ejaculation*, ejaculation failure* Ejaculation disorder*, sexual dysfunction Post partum haemorrhage
General disorders and administrative site conditions	Frequent	Fatigue, chills, fever, asthenia, feeling jittery, irritability
Investigations	Frequent Less frequent	Increased weight, increased blood pressure, decreased weight Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin

* Frequency calculated based on men only.

****** see section 4.4.

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 providers 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

Signs and symptoms:

There is limited clinical experience with desvenlafaxine overdosage in humans.

Management of overdose:

No specific antidotes for EXLOV XR are known. Induction of emesis is not recommended. Because of the moderate volume of distribution of this medicine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended.

Activated charcoal should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX23

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants).

Non-clinical studies have shown that desvenlafaxine succinate is a selective serotonin and norepinephrine reuptake inhibitor (SNRI).

The clinical efficacy of desvenlafaxine in the treatment of major depressive disorder is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H_1-histaminergic, or α_1-adrenergic receptors *in vitro*. In the same comprehensive binding profile assay, desvenlafaxine also lacked significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacked monoamine oxidase (MAO) inhibitory activity.

Desvenlafaxine lacked significant activity in the *in vitro* cardiac potassium channel (hERG) assay.

5.2 Pharmacokinetic properties

The single-dose pharmacokinetics of desvenlafaxine is linear and dose-proportional in a dose range of 50 mg to 600 mg/day. The mean terminal half-life, $t_{1/2}$ is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 - 5 days. At steady state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

There is a statistically significant increase in exposure in females compared to males (C_{max} 18 - 37 % greater; AUC 6 - 17 % greater).

Absorption and distribution

Desvenlafaxine is well absorbed, with an absolute oral bioavailability of 80 %. Mean time to peak plasma concentrations (T_{max}) is about 7,5 hours after oral administration. AUC and C_{max} of 6,747 ng.hr/ml and 376 ng/ml, respectively, are predicted after a single dose of 100 mg.

Effects of food

The C_{max} of desvenlafaxine has been shown to increase by about 16 % when taken with food, while AUCs are similar under both fed and fasting conditions (high-fat meal) in healthy subjects. This difference is not clinically significant; therefore, desvenlafaxine can be taken without regard to meals.

The plasma protein binding of desvenlafaxine is low (30 %) and is independent of medicine concentration. Desvenlafaxine's volume of distribution at steady-state following intravenous administration is 3,4 l/kg, indicating distribution into nonvascular compartments.

Metabolism and elimination

Approximately 45 % of desvenlafaxine is excreted unchanged in urine.

Desvenlafaxine is primarily metabolised by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2Bl7) and to a minor extent through oxidative metabolism. Approximately 19 % of the

administered dose is excreted as the glucuronide metabolite and < 5 % as the oxidative metabolite (N, O-didesmethylvenlafaxine) in urine.

CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Pharmacokinetics in special patient groups

Elderly population

In a trial of healthy subjects administered doses up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32 % increase in C_{max} and a 55 % increase in AUC values in subjects greater than 75 years of age, as compared with subjects 18 to 45 years of age. No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see sections 4.2 and section 4.4).

Patients with renal impairment

The pharmacokinetics of a single dose of desvenlafaxine succinate 100 mg were studied in subjects with mild (CrCl 50-80 ml/min) (n=9), moderate (CrCl 30-50 ml/min) (n=8), severe (CrCl<30 ml/min) (n=7), end-stage renal disease (ESRD) (n=9) requiring dialysis and to healthy, age-matched control subjects (n=8).

The elimination was significantly correlated with creatinine clearance. A 29 % reduction in total body clearance has been observed in patients with mild creatinine clearance; 39 % in moderate renal impairment, 51 % in severe and 58 % in end-stage renal disease (ESRD) when compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42 % in mild, 56 % in moderate, 108 % in severe and 116 % in ESRD subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11,1 hours in the healthy subjects to 13,5, 15,5, 17,6 and 22,8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively.

Less than 5 % of the medicine in the body was cleared during a standard 4-hour haemodialysis procedure. Therefore, supplemental doses should not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant impairment of renal function (see sections 4.2 and 4.4).

Patients with hepatic impairment

The pharmacokinetics of desvenlafaxine 100 mg were studied subjects with mild (Child-Pugh A, n=8), moderate (Child-Pugh B, n=8) and severe (Child-Pugh C, n=8) hepatic impairment and in healthy subjects (n=12).

When compared to healthy subjects, the average AUC was increased by approximately 31 % and 35 % in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Less than 5 % difference was observed between subjects with mild hepatic impairment and healthy subjects.

Systemic clearance (CL/F) was decreased by approximately 20 % and 36 % in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5 % difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively (see section 4.2).

QTc trial

When studied with prospectively determined criteria, neither QT prolongation, nor an effect on QRS interval, was observed in healthy women taking desvenlafaxine.

Paediatric population

Safety and efficacy in patients less than 18 years of age have not been established.

5.3 Preclinical safety data

Genotoxicity

Desvenlafaxine was not genotoxic in in vitro assays for bacterial gene mutation, mammalian gene mutation, chromosomal aberrations and cell transformation, or in in vivo tests for clastogenic activity in mice and rats.

Carcinogenicity

Desvenlafaxine succinate did not increase the incidence of tumours in long-term mouse and rat carcinogenicity studies at oral doses up to 7 (mice), 14 (male rats) and 23 (female rats) times the maximal recommended human dose of 200 mg/day, on a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Hypromellose

Microcrystalline cellulose

Stearic acid

Talc

Coating:

FD&C Yellow #6/ Sunset Yellow FCF Aluminium Lake (100 mg tablet only)

Iron oxide red

Iron oxide yellow (50 mg tablet only)

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide

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

EXLOV XR tablets are packed in clear PVC/Aclar Aluminium foil blister packs, inside a carton.

Each carton contains 30 tablets.

6.6 Special precautions for disposal

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 NUMBER(S)

Exlov XR 50 mg: A51/1.2/0009

Exlov XR 100 mg: A51/1.2/0010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 18 August 2020

Revision date: 05 October 2021