SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

EXSIRA 50 mg Extended–release tablet

EXSIRA 100 mg Extended–release tablet

COMPOSITION:

Each EXSIRA 50 mg extended-release film-coated tablet contains desvenlafaxine succinate equivalent to 50 mg desvenlafaxine.

Each EXSIRA 100 mg extended-release film-coated tablet contains desvenlafaxine succinate equivalent to 100 mg desvenlafaxine.

Sugar free.

Excipients: Hypromellose, microcrystalline cellulose, talc, magnesium stearate, and a film-coating containing:

EXSIRA 50 mg – Polyvinyl alcohol, part hydrolysed; titanium dioxide; macrogol/PEG 3350; talc; yellow iron oxide; red iron oxide;

EXSIRA 100 mg – Polyvinyl alcohol, part hydrolysed; titanium dioxide; macrogol/PEG 3350; talc; red iron oxide; FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake.

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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:

A food-effect trial involving administration of desvenlafaxine to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the C_{max} was increased about 16 % in the fed state, while the AUCs were similar. 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 drug 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 UGT2B17) 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.

Geriatric:

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 DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

Paediatric:

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

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). Elimination was significantly correlated with creatinine clearance. Total body clearance was reduced by 29 % in mild, 39 % in moderate, 51 % in severe renal impairment, and 58 % in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42 % in mild, 56 % in moderate, 108 % in severe (24-hr CrCl < 30 ml/min), 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 DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

Patients with hepatic impairment:

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in 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).

Average AUC was increased by approximately 31 % and 35 % in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were

comparable in subjects with mild hepatic impairment and healthy subjects (< 5 % difference).

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 DOSAGE AND DIRECTIONS FOR USE).

QTc trial:

In a QTc study with prospectively determined criteria, in healthy women, desvenlafaxine did not cause QT prolongation. Additionally, no effect on QRS interval was observed.

INDICATIONS:

Major depressive disorder:

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

CONTRAINDICATIONS:

Hypersensitivity to EXSIRA, venlafaxine hydrochloride or to any excipients in the EXSIRA formulation.

EXSIRA is an inhibitor of both norepinephrine and serotonin reuptake. EXSIRA must not be used in combination with a monoamine oxidase inhibitor (MAOI), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of EXSIRA, at least 7 days should be allowed after stopping EXSIRA before starting an MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines such as EXSIRA 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 INTERACTIONS).

Children less than 18 years of age, as safety and efficacy have not been established (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

Pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

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 EXSIRA 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 EXSIRA 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, EXSIRA should be tapered (see DOSAGE AND DIRECTIONS FOR USE).

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 age 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.

Paediatric use:

Safety and efficacy in children under 18 years of age has not been established (see CONTRAINDICATIONS and SIDE EFFECTS). In clinical trials 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 (see CONTRAINDICATIONS).

Mania/hypomania:

In clinical trials, mania was reported for 0,03 % of patients treated with EXSIRA. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. EXSIRA should be used cautiously in patients with a history or family history of mania or hypomania (see SIDE EFFECTS).

Serotonin syndrome:

The development of a potentially life-threatening serotonin syndrome may occur with EXSIRA 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 INTERACTIONS).

The concomitant use of EXSIRA with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma:

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

Ischaemic cardiac adverse events:

In clinical trials, there were uncommon reports of ischaemic cardiac adverse events, including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation; these patients had multiple underlying cardiac risk factors. More patients experienced these events during EXSIRA 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 DOSAGE AND DIRECTIONS FOR USE).

Adverse reactions leading to discontinuation of therapy:

The most common adverse reaction leading to discontinuation in at least 2 % of the EXSIRA-treated patients in the short-term trials, up to 12 weeks, was nausea (2 %); in the 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 EXSIRA, it is an adverse reaction for other SNRIs and may also occur with EXSIRA.

Effects on activities requiring concentration and performance:

Interference with cognitive and motor performance:

The results of a clinical trial that assessed the effects of EXSIRA on behavioural performance of healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behaviour performance. However, since any 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 EXSIRA therapy does not adversely affect their ability to engage in such activities.

Abuse and dependence:

Physical and psychological dependence:

Although EXSIRA has not been systematically studied in preclinical or clinical trials for its potential for abuse, no indication of drug-seeking behaviour was seen in the clinical trials.

Co-administration of medicines containing venlafaxine and/or EXSIRA:

EXSIRA is the major active metabolite of venlafaxine, a medication used to treat major depressive, generalised anxiety, social anxiety and panic disorders. EXSIRA should not be used concomitantly with products containing venlafaxine hydrochloride or other products containing EXSIRA.

Effects on blood pressure:

Increased blood pressure:

Increases in blood pressure were observed in some patients in clinical trials, particularly with higher doses. Pre-existing hypertension should be controlled before treatment with EXSIRA. Patients receiving EXSIRA should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with EXSIRA. Sustained blood pressure

increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving EXSIRA, 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 SIDE EFFECTS).

Postural hypotension (see Geriatric use).

Cardiovascular/cerebrovascular:

Caution is advised in administering EXSIRA to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and heart rate were observed in clinical trials with EXSIRA. EXSIRA 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 cerebrovascular disease, were excluded from clinical trials (see SIDE EFFECTS).

Serum lipids:

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical trials. Measurement of serum lipids should be considered during treatment with EXSIRA (see SIDE EFFECTS).

Seizures:

Cases of seizure were reported in pre-marketing clinical trials with EXSIRA. EXSIRA has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical trials. EXSIRA should be prescribed with caution in patients with a seizure disorder (see SIDE EFFECTS).

Discontinuation effects:

During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors) such as EXSIRA, there have been spontaneous reports of adverse events occurring upon discontinuation of these medicines, particularly when abrupt, including the following: 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. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored when discontinuing treatment with EXSIRA. 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 (see DOSAGE AND DIRECTIONS FOR USE and SIDE EFFECTS).

Abnormal bleeding:

Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation. As with other agents that inhibit serotonin-reuptake, EXSIRA 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 EXSIRA, usually in volume-depleted or dehydrated patients, including elderly patients and patients taking diuretics (see SIDE EFFECTS).

Geriatric use:

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of EXSIRA should be considered when determining dose (see DOSAGE AND DIRECTIONS FOR USE and PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Of the 7 785 patients in pre-marketing clinical trials with EXSIRA, 5 % of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled trials, there was a higher incidence of systolic orthostatic hypotension in patients treated with EXSIRA 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 trials, there were increases in systolic blood pressure in patients ≥ 65 years of age compared to patients < 65 years of age treated with EXSIRA.

Effects on ability to drive and use machines:

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

INTERACTIONS:

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 EXSIRA (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 EXSIRA in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS AND SPECIAL PRECAUTIONS and CONTRAINDICATIONS).

Central nervous system (CNS)-active agents:

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

Serotonin syndrome:

Serotonin syndrome, a potentially life-threatening condition, may occur with EXSIRA treatment, particularly with concomitant use of other agents 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 CONTRAINDICATIONS), 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 WARNINGS AND SPECIAL PRECAUTIONS).

Ethanol:

Patients should be advised to avoid alcohol consumption while taking EXSIRA.

Potential for other medicines to affect EXSIRA:

Inhibitors of CYP3A4:

CYP3A4 is involved in EXSIRA elimination. In a clinical trial, ketoconazole (200 mg twice daily) increased the area under the concentration vs. time curve (AUC) of EXSIRA (400 mg single dose) by approximately 43 %, a weak interaction and C_{max} by about 8 %. Concomitant use of EXSIRA with potent inhibitors of CYP3A4 may result in higher exposure to EXSIRA.

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 EXSIRA.

Potential for EXSIRA to affect other medicines:

Medicines metabolised by CYP2D6:

Clinical trials have shown that EXSIRA is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. When EXSIRA 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 EXSIRA 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 EXSIRA 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, EXSIRA does not inhibit or induce the CYP3A4 isozymes. In a clinical trial, when EXSIRA was administered (at a dose of 400 mg daily) in conjunction with a single 4 mg dose of midazolam, a CYP3A4 substrate, the AUC of midazolam decreased by approximately 31 %. In a second study, EXSIRA 50 mg daily was co-administered with a single 4 mg dose of midazolam. The AUC and C_{max} of midazolam decreased by approximately 29 % and 14 %, respectively. Concomitant use of EXSIRA 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):

Clinical studies have shown that EXSIRA (100 mg daily) does not have a 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 metabolites 4-hydroxy-tamoxifen and endoxifen primarily by CYP2D6 with minor contributions to metabolism by CYP3A4, was administered in conjunction with EXSIRA (100 mg daily). The AUC increased by 3 % with concomitant administration of EXSIRA. The AUC of 4-hydroxy-tamoxifen increased by 9 %. Endoxifen AUC was decreased by 12 %.

EXSIRA 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 EXSIRA. The AUC of dehydro-aripiprazole increased by 3 %, with concomitant administration.

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

In vitro, EXSIRA does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of medicines that are metabolised by these CYP isozymes.

P-glycoprotein transporter:

In vitro, EXSIRA is not a substrate or an inhibitor for the P-glycoprotein transporter.

Laboratory test interactions:

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

Electroconvulsive therapy:

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with EXSIRA treatment for MDD.

PREGNANCY AND LACTATION:

EXSIRA must not be administered to pregnant or lactating women. Safety during human pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy:

The safety of EXSIRA in human pregnancy has not been established. If EXSIRA 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:

EXSIRA (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious

adverse reactions in nursing infants from EXSIRA, a decision should be made whether or not to discontinue nursing or to discontinue EXSIRA, taking into account the importance of the medicine to the mother.

DOSAGE AND DIRECTIONS FOR USE:

Major depressive disorder:

The recommended dose for EXSIRA 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.

Use in patients with renal impairment:

The recommended starting dose in patients with severe renal impairment (24-hr CrCl < 30ml/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 PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Use in patients with hepatic impairment:

No dosage adjustment is necessary for patients with hepatic impairment (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Paediatric use:

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

Use in elderly patients:

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of EXSIRA should be considered when determining dose (see PHARMACOLOGICAL ACTION, Pharmacokinetic properties – *Geriatrics*).

Discontinuing EXSIRA:

Symptoms associated with discontinuation of EXSIRA, 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 WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

Switching patients from other antidepressants to EXSIRA:

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to EXSIRA. Tapering of the initial antidepressant may be necessary to minimise discontinuation symptoms.

SIDE EFFECTS:

Adverse reactions are categorised by body system and listed in order of decreasing frequency using the following definitions:

Expected frequency of adverse reactions is presented in CIOMS frequency categories: Very common: ≥ 10 %, Common: ≥ 1 % and < 10 %, Uncommon: ≥ 0,1 % and < 1 %, Rare: ≥ 0,01 % and < 0,1 %, Very rare: < 0,01 %.

System Organ Class	**Frequency**	**Side effect**
Cardiac disorders	Common	Palpitations, tachycardia
Ear and labyrinth disorders	Common	Tinnitus
Eye disorders	Common	Blurred vision, mydriasis
Gastrointestinal disorders	Very common	Nausea, dry mouth, constipation
	Common	Diarrhoea, vomiting
General disorders and administration site conditions	Common	Fatigue, chills, asthenia, feeling jittery, irritability
Immune system disorders	Uncommon	Hypersensitivity
Investigations	Common	Increased weight, increased blood pressure, decreased weight
	Uncommon	Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin
Metabolism and nutritional disorders	Common	Decreased appetite
	Rare	Hyponatraemia
Musculoskeletal, connective tissue	Common	Musculoskeletal stiffness

and bone disorders		
Nervous system disorders	Very common	Dizziness, headache
	Common	Somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention, vertigo
	Uncommon	Syncope
	Rare	Convulsion, dystonia
Psychiatric disorders	Very common	Insomnia
	Common	Anxiety, abnormal dreams, nervousness, decreased libido, anorgasmia
	Uncommon	Withdrawal syndrome, abnormal orgasm, depersonalisation
	Rare	Hypomania, hallucinations
Renal and urinary disorders	Uncommon	Urinary hesitation, proteinuria, urinary retention
Reproductive system and breast disorders	Common	Erectile dysfunction*, delayed ejaculation*, ejaculation failure*
	Uncommon	Ejaculation disorder*, sexual dysfunction
Respiratory, thoracic and mediastinal disorders	Common	Yawning
	Uncommon	Epistaxis
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Common	Rash
	Uncommon	Alopecia
	Rare	Photosensitivity reaction, angioedema
	Not known	Stevens-Johnson syndrome**
Vascular disorders	Common	Hot flush
	Uncommon	Orthostatic hypotension (see WARNINGS AND SPECIAL PRECAUTIONS), peripheral coldness

*Frequency is calculated based on men only

**Adverse reaction identified during post-approval use

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is limited clinical experience with EXSIRA overdosage in humans.

No specific antidotes for EXSIRA are known. Induction of emesis is not recommended. Because of the moderate volume of distribution of this medicine, forced diuresis, dialysis, haemoperfusion, 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. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered.

IDENTIFICATION:

EXSIRA 50 mg extended-release tablets are light pink, square (pyramid, one sided), film-coated tablets, debossed “W” over “50” on the flat side.

EXSIRA 100 mg extended-release tablets are reddish-orange, square (pyramid, one sided), film-coated tablets, debossed “W” over “100” on the flat side.

PRESENTATION:

EXSIRA (desvenlafaxine succinate) extended-release tablets are available as follows:

A carton containing one or more clear plastic/aluminium foil blister strips containing 7, 14 or 28 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep out of reach of children. Keep well closed.

Do not remove blister card from the carton until required for use.

REGISTRATION NUMBER:

EXSIRA 50 mg: 42/1.2/0935

EXSIRA 100 mg: 41/1.2/0427

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

06 March 2014