SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

EXSIRA 50 mg Extended–release tablets

EXSIRA 100 mg Extended–release tablets

2. QUALITATIVE AND QUANTITATIVE 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive disorder

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

4.2 Posology and method of administration

Posology

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.

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 sections 4.4 and 4.8).

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.

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).

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 section 5.2 – *Elderly*).

Paediatric population

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

Method of administration

For oral use.

4.3 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 section 4.5).
- Children less than 18 years of age, as safety and efficacy have not been established (see sections 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see section 4.6 and 4.8).

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 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 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.

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 section 4.8).

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 section 4.5).

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 section 4.8).

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 section 4.2).

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 medicine 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 section 4.8).

Postural hypotension (see Use in elderly patients).

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 section 4.8).

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 section 4.8).

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 section 4.8).

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 sections 4.2 and 4.8).

Abnormal bleeding

Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation. As with other medicines 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 section 4.8).

Interstitial lung disease and eosinophilic pneumonia

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent medicine of EXSIRA) therapy have been reported. The possibility of these adverse events should be considered in patients treated with EXSIRA who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of EXSIRA should be considered.

Special populations

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 sections 4.2 and 5.2).

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.

Paediatric population

Safety and efficacy in children under 18 years of age has not been established (see sections 4.3 and 4.8). 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 section 4.3).

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 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 MAOIs, including selegiline and linezolid [an antibiotic which is a reversible non-selective MAOI], is contraindicated (see sections 4.3 and 4.4).

Central nervous system (CNS)-active medicines

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 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, 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 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 Cmax 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.

4.6 Fertility, pregnancy and lactation

EXSIRA must not be administered to pregnant or lactating women. Safety during human pregnancy and lactation has not been established (see section 4.3).

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.

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 and 4.8).

Breastfeeding

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.

4.7 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions

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**
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutritional disorders	Common	Decreased appetite
	Rare	Hyponatraemia
Psychiatric disorders	Very common	Insomnia
	Common	Anxiety, abnormal dreams, nervousness, decreased libido, anorgasmia
	Uncommon	Withdrawal syndrome, abnormal orgasm, depersonalisation
	Rare	Hypomania, hallucinations
Nervous system disorders	Very common	Dizziness, headache
	Common	Somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention, vertigo
	Uncommon	Syncope
	Rare	Convulsion, dystonia
Eye disorders	Common	Blurred vision, mydriasis
Ear and labyrinth	Common	Tinnitus

disorders		
Cardiac disorders	Common	Palpitations, tachycardia
Vascular disorders	Common	Hot flush
	Uncommon	Orthostatic hypotension (see section 4.4), peripheral coldness
Respiratory, thoracic and mediastinal disorders	Common	Yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea, dry mouth, constipation
	Common	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Common	Rash
	Uncommon	Alopecia
	Rare	Photosensitivity reaction, angioedema
	Not known	Stevens-Johnson syndrome**
Musculoskeletal, connective tissue and bone disorders	Common	Musculoskeletal stiffness
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
	Not known	Postpartum haemorrhage***
General disorders and	Common	Fatigue, chills, asthenia, feeling jittery, irritability

administration site conditions		
Investigations	Common	Increased weight, increased blood pressure, decreased weight
	Uncommon	Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin

*Frequency is calculated based on men only

**Adverse reaction identified during post-approval use

***This event has been reported for the therapeutic class of SSRIs/SNRIs (see section 4.4 and 4.6)

Post-marketing experience

The following adverse reactions have been identified during post-approval use of EXSIRA.

System organ class	**Undesirable effect**
Gastrointestinal disorders	Acute pancreatitis

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 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 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.

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.

Special populations

Elderly

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 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). 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 sections 4.2 and 4.4).

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 section 4.2).

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EXSIRA 50 mg extended-release tablets

Tablet core

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Talc

Film-coating

Macrogol/PEG 3350

Polyvinyl alcohol, part hydrolysed

Red iron oxide

Talc

Titanium dioxide

Yellow iron oxide

EXSIRA 100 mg extended-release tablets

Tablet core

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Talc

Film-coating

Macrogol/PEG 3350

Polyvinyl alcohol, part hydrolysed

Red iron oxide

Talc

Titanium dioxide

Yellow iron oxide

FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep well closed.

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

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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8. REGISTRATION NUMBERS

EXSIRA 50 mg: 42/1.2/0935

EXSIRA 100 mg: 41/1.2/0427

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10. DATE OF REVISION OF THE TEXT

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