SCHEDULING STATUS

S5

1. **NAME OF MEDICINE:**

   DESLAFEKS 50 mg, (EXTENDED RELEASE FILM COATED TABLETS)

   DESLAFEKS 100 mg, (EXTENDED RELEASE FILM COATED TABLETS)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   Each extended release tablet of **DESLAFEKS** contains desvenlafaxine succinate equivalent to 50 mg desvenlafaxine.

   Each extended release tablet of **DESLAFEKS** 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 film coated tablets

DESLAFEKS Tablets 50mg:

Light pink coloured, round, biconvex tablets, debossed with ‘L349’ on one side and plain on other side

DESLAFEKS Tablets 100mg:

Dark brown to red coloured, round, biconvex tablets, debossed with ‘L350’ on one side and plain on other side

4. **CLINICAL PARTICULARS**

   4.1 Therapeutic Indications

   Major Depressive disorder: **DESLAFEKS** 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 **DESLAFEKS** 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 impairments: No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Elderly population:

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 “section 5.2: Geriatrics”).

Paediatric population:

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

Discontinuing DESLAFEKS:

Symptoms associated with the discontinuation of **DESLAFEKS,** 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 should be considered. The medical practitioner may continue decreasing the dose but at a more gradual rate (see section 4.4 and 4.8).

Switching patients from other antidepressants to **DESLAFEKS**:

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

Method of administration:

DESLAFEKS is for oral use. **DESLAFEKS** should be taken at approximately the same time each day. The tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved'

4.3 Contraindications

- Hypersensitivity to desvenlafaxine, venlafaxine hydrochloride or to any excipients in the **DESLAFEKS** formulation.
- **DESLAFEKS** is an inhibitor of both noradrenaline (norepinephrine) and serotonin uptake. **DESLAFEKS** 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 desvenlafaxine, as contained in **DESLAFEKS,** at least 7 days should be allowed after stopping **DESLAFEKS** before starting an MAOI.

Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines such as **DESLAFEKS** 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 sections 4.4 and 4.5).

- **DESLAFEKS** is contraindicated in children under age of 18 years 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

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

Patients with major depression disorder may experience worsening of their depression and /or 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 inducing such behaviour has not been established. Patients being treated with **DESLAFEKS** should nevertheless, be observed closely for clinical worsening and suicide tendencies, 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 disorders 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 regime, including possibly discontinuing **DESLAFEKS** in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms. If the decision is made to discontinue treatment, **DESLAFEKS** should be tapered (see section 4.2).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Data does not show an increase in the risk of suicidality with antidepressants in adults beyond the age of 24 years; there is a reduction in the risk of suicidality in adults aged 65 years and older.

Paediatric use:

Safety and efficacy in children under 18 years of age has not been established (see section 4.3 and 4.8). In major depressive disorder, there are increased reports of hostility and suicide related adverse events such as suicidal ideation and self-harm

Mania /hypomania:

Mania is reported for 0.03 % of patients treated with **DESLAFEKS.**

Activation of mania/ hypomania has also been reported in a small proportion of patients with major depressive disorder who were treated with other antidepressants. **DESLAFEKS** should be used cautiously in patients with a history of family history of mania or hypomania (see section 4.8).

DESLAFEKS is an inhibitor of both noradrenaline (norepinephrine) and serotonin reuptake. **DESLAFEKS** 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 **DESLAFEKS,** at least 7 days should be allowed after stopping **DESLAFEKS** before starting an MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SSNRI medicines such as **DESLAFEKS** 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 sections 4.3 and 4.5).

Serotonin syndrome:

The development of a potentially life-threatening serotonin syndrome may occur with **DESLAFEKS** treatment, particularly with concomitant use of other serotonergic medicines (including SSRI's, 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. hyperflexia, incoordination) and /or gastrointestinal symptoms (e.g. nausea, vomiting and diarrhoea) (see section 4.5).

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

Narrow-angle glaucoma:

Mydriasis has been reported in association with **DESLAFEKS,** 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:

There are less frequent reports of ischaemic cardiac adverse events, including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation; these patients have multiple underlying events during **DESLAFEKS** treatment as compared to placebo.

Pregnancy and lactation:

DESLAFEKS must not be administered to pregnant or lactating women. The safety of **DESLAFEKS** in human pregnancy has not been established. If **DESLAFEKS** is used until, or shortly before birth, discontinuation effects in the new-born may occur. (see sections 4.3 and 4.6)

Adverse reactions reported with other SNRIs:

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

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

Desvenlafaxine is the major active metabolite for venlafaxine, a medication used to treat major depression, generalised anxiety, social anxiety and panic disorder.

DESLAFEKS should not be used concomitantly with other products containing venlafaxine hydrochloride or other products containing desvenlafaxine.

Effects on blood pressure: Increased blood pressure: Increases in blood pressure were observed in some patients, particularly with higher doses. Pre - existing hypertension should be controlled before treatment with **DESLAFEKS.** Patients receiving **DESLAFEKS** should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with **DESLAFEKS.** Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving **DESLAFEKS,** either dose reduction or discontinuation should be considered.

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

Postural hypotension: (see “Elderly use”)

Cardiovascular/ cerebrovascular:

Caution is advised in administering **DESLAFEKS** to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and heart rate were observed with **DESLAFEKS. DESLAFEKS** 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 tests. (see section 4.8)

Serum lipids:

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides are observed. Measurement of serum lipids should be considered during treatment with **DESLAFEKS** (see section 4.8).

Seizures: DESLAFEKS should be prescribed with caution in patients with a seizure disorder (see section 4.8).

Discontinuation effects:

Discontinuation effects of **DESLAFEKS** particularly when abrupt, includes 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 are reports of serious discontinuation symptoms.

Patients should be monitored when discontinuing treatment with **DESLAFEKS.** 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).

Adverse reactions leading to discontinuation of therapy:

The most frequent adverse reaction leading to discontinuation in at least 2 % of the **DESLAFEKS** -treated patients in short term trials, up to 12 weeks is nausea; in the long-term studies, up to 11 months, no events lead to discontinuation in at least 2 % of the patients.

Abnormal bleeding:

Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggression. As with other medicines that inhibits serotonin-reuptake, **DESLAFEKS** should be used cautiously in patients predisposed to bleeding.

Hyponatraemia:

Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretics Hormone (SIADH) secretion have occurred with SNRIs and SSRIs, including **DESLAFEKS**, usually in volume-depleted or hydrated 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 compound of desvenlafaxine as contained in **DESLAFEKS)** have been reported. The possibility of these adverse events should be considered in patients treated with **DESLAFEKS** who present with progressive dyspnoea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of **DESLAFEKS** should be considered.

Physical and psychological dependence

Although **DESLAFEKS** has not been systematically studied for its potential for abuse, no indication of drug-seeking behaviour have been documented'.

Elderly use:

No dosage adjustment is required solely on the basis of age, however, possible reduced renal clearance of **DESLAFEKS** should be considered when determining dose (see section 4.2 and section 5.2). There are increases in systolic blood pressure in patients ≥ 65 years of age compared to patients < 65 years of age treated with **DESLAFEKS**.

4.5 Interaction with other medicines and other forms of interaction

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 antidepressant with pharmacological properties similar to **DESLAFEKS** (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 **DESLAFEKS** in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see sections 4.3 and 4.4).

Central nervous system (CNS)- active medicines:

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

Serotonin syndrome: Serotonin syndrome, a potentially life-threatening condition, may occur with **DESLAFEKS** 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 with taking **DESLAFEKS.**

Potential for other medicines to affect DESLAFEKS: Inhibitors of CYP3A4:

CYP3A4 is involved in desvenlafaxine elimination. Concomitant use of **DESLAFEKS** with potent inhibitors of CYP3A4 like ketoconazole may result in higher exposure to **DESLAFEKS.**

Potential for DESLAFEKS to affect other medicines: Medicines metabolised by CYP2D6:

DESLAFEKS is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. Concomitant use of **DESLAFEKS** with medicine metabolised by CYP2D6 may result in increased concentrations of its CYP2D6 metabolites.

Medicines metabolised by CYP3A4:

In vitro, **DESLAFEKS** does not inhibit or induce the CYP3A4 isozymes. Concomitant use of **DESLAFEKS** with a medicine metabolised by CYP3A4 may result in lower exposure to that medicine.

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

DESLAFEKS (100 mg daily) does not have a clinically relevant effect on medicines metabolised by a combination of both CYP2D6 and CYP3A4 enzymes.

The AUC of aripiprazole increased by 6 %, with concomitant administration of **DESLAFEKS**. The AUC dehydro-aripiprazole increased by 3 %, with concomitant administration.

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

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

Laboratory test interactions:

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

Electroconvulsive therapy:

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

4.6 Fertility, pregnancy and lactation

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

Women of childbearing potential/Contraception in males and females

Careful consideration should be given to using **DESLAFEKS** in women of productive potential and these patients should be advised to avoid pregnancy while they are taking the medicines.

Pregnancy

The safety of **DESLAFEKS** in human pregnancy has not been established. If **DESLAFEKS** is used until, or shortly before birth, discontinuation effects in the new-born 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. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. (see section 5.2). Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Breast feeding

DESLAFEKS (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from **DESLAFEKS,** a decision should be made whether or not to discontinue nursing or to discontinue **DESLAFEKS,** taking into account the importance of the medicine to the mother.

Fertility:

See section 5.3.

4.7 Effects on ability to drive and use machines

DESLAFEKS 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

Immune system disorders:

Less frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Decreased appetite

Less frequent: Hyponatraemia

Psychiatric disorders:

*Frequent***:** Insomnia, anxiety, abnormal dreams, nervousness, decreased, libido, anorgasmia

*Less frequent***:** Withdrawal syndrome, abnormal orgasm, depersonalisation, hypomania, hallucinations

Frequency unknown: In children, reports of hostility, suicidal ideation and self-harm

Nervous system disorders:

Frequent: Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia

Less frequent: Disturbance in attention, vertigo, syncope, convulsion, dystonia

Eye disorders

Frequent: Blurred vision, mydriasis

Ear and labyrinth disorders:

Frequent: Tinnitus

Cardiac disorders:

Frequent: Palpitations, tachycardia

Vascular disorders:

Frequent: Hot flush

Less frequent: Orthostatic hypotension, peripheral coldness

Respiratory, thoracic and mediastinal disorders

Frequent: Yawning

Less frequent: Epistaxis

Gastrointestinal disorders:

Frequent: Nausea, dry mouth, constipation, diarrhoea, vomiting

Reproductive system and breast disorders:

Frequent: Erectile dysfunction, delayed ejaculation, ejaculation failure

Less frequent: Ejaculation disorder, sexual dysfunction

Skin and subcutaneous tissue disorders:

Frequent: Hyperhidrosis, rash

Less frequent: Alopecia, Photosensitivity reaction, angioedema

Not known: 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: Erectile dysfunction, delayed ejaculation, ejaculation failure

Less frequent: Ejaculation disorder, sexual dysfunction

General disorders and administration site conditions:

Frequent: Fatigue, chills, asthenia, feeling jittery, irritability

Investigations:

Frequent: Increased weight, increased blood pressure, decreased weight

Less frequent: Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin.

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

There is limited clinical experience with **DESLAFEKS** overdosage in humans.

No specific antidotes for **DESLAFEKS** 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 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

Category and Class: Psychoanaleptics (antidepressants) A 1.2

Non-clinical studies have shown that desvenlafaxine succinate is a selective serotonin and noradrenaline (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 (MOA) inhibitory activity. Desvenlafaxine lacked significant activity in the *in vitro* cardiac potassium channel (hERG) assay.

5.2 Pharmacokinetic properties

Absorption:

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 administration . AUC and C_{max} of 6747 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 patients under fasting and fed conditions (high-fat meal) indicated that the C_{max} was increased about 16 % in the fed state, while the AUC's were similar. This difference is not clinically significant, therefore, desvenlafaxine can be taken without regards 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

Desvenlafaxine is primarily metabolised by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15 and UGT2B17) and to a minor extent through oxidation metabolism. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Elimination:

Approximately 45 % of desvenlafaxine is excreted unchanged in urine. Approximately 19 % of the administrated dose is excreted as the glucuronide metabolite and < 5 % as the oxidative metabolite (N, O-didesmethylvenlafaxine) in urine.

Linearity

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). 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 non-vascular compartments.

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 Cmax 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 patients 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 patients (n=8). Elimination was significantly correlated with creatine 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 patients. 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 (t1/2) 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 patients 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 patients (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 patients with mild hepatic impairment and healthy patients (< 5 % difference). Systemic clearance (CL/F) was decreased by approximately 20 % and 36 % in patients with moderate and severe hepatic impairment, respectively. CL/F values were comparable in mild hepatic impairment and healthy patients (< 5 % difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy patients and patients 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.

5.3 Pre-Clinical safety data

Carcinogenesis

Desvenlafaxine administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumours in either study.

Mutagenesis

Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

Impairment of fertility

Reduced fertility was observed in a study in which both male and female rats received desvenlafaxine. This effect was noted at oral doses approximately 10 times a human dose of 100 mg/day on a mg/m^2 basis. There was no effect on fertility at oral doses approximately 3 times a human dose of 100 mg/day on a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Hypromellose, microcrystalline cellulose, povidone, talc, magnesium stearate, titanium dioxide, macrogol, iron oxide red and iron oxide black.

6.2 Incompatibilities

None

6.3 Shelf life

24 months after manufacturing.

6.4 Special Precautions for storage

Store at or below 30 °C. Keep well closed. Protect from moisture and light.

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

6.5 Nature and contents of container

DESLAFEKS extended- release tablets are available as follows: A carton containing one or more aluminium/aluminium foil blister strips containing 7, 14 or 28 tablets each.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be returned to the pharmacy for destruction or it must be disposed of in accordance with local requirements for medical waste destruction.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. REGISTRATION NUMBERS

A 52/1.2/0583

A 52/1.2/0584

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 April 2021

10. DATE OF REVISION OF THE TEXT

TBI