PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

DENLAZYD 50 extended-release tablets

DENLAZYD 100 extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each DENLAZYD 100 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.

DENLAZYD 50 extended-release tablets are light pink, oval, film-coated tablets, with a matte appearance and debossed with “50” on one side and plain on the other side.

DENLAZYD 100 extended-release tablets are orange to reddish orange, oval, film-coated tablets, with a matte appearance and debossed with “100” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive disorder

DENLAZYD 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 DENLAZYD 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 DENLAZYD

Symptoms associated with discontinuation of DENLAZYD, other serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (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 DENLAZYD

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to DENLAZYD. 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-hour creatinine clearance < 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 DENLAZYD should be considered when determining the dose (see section 5.2).

Paediatric population

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

Method of administration:

For oral use.

The film-coated tablet should not be broken because the coating is intended to ensure an extended release.

4.3 Contraindications

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any of the excipients in DENLAZYD (see section 6).
- DENLAZYD is an inhibitor of both norepinephrine and serotonin reuptake. DENLAZYD 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 DENLAZYD, at least 7 days should be allowed after stopping DENLAZYD before starting an MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines, such as DENLAZYD, 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 sections 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 DENLAZYD 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 nonpsychiatric 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 DENLAZYD 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, DENLAZYD should be tapered (see section 4.2).

Short-term trials have not shown an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of

suicidality with antidepressants compared to placebo in adults aged 65 years and older.

Mania/hypomania

There have been reports of mania in patients treated with desvenlafaxine, as in DENLAZYD. 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. DENLAZYD 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 DENLAZYD 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 DENLAZYD with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

Mydriasis has been reported in association with DENLAZYD; 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

Ischaemic cardiac adverse events have been reported less frequently including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo.

Discontinuation symptoms

Adverse reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment 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 was nausea.

Adverse reactions reported with other SNRIs

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

Abuse and dependence

Physical and psychological dependence

Although DENLAZYD has not been systematically studied for its potential for abuse, no indication of medicine-seeking behaviour has been seen.

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

DENLAZYD is the major active metabolite of venlafaxine, a medicine used to treat major depressive, generalised anxiety, social anxiety and panic disorders. DENLAZYD should not be used concomitantly with medicines containing venlafaxine hydrochloride or other medicines containing DENLAZYD (see section 4.5).

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 DENLAZYD. Patients receiving DENLAZYD should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with DENLAZYD. Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving DENLAZYD, 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).

Cardiovascular/cerebrovascular disorders

Caution is advised in administering DENLAZYD to patients with cardiovascular, cerebrovascular or lipid metabolism disorders. Increases in blood pressure and heart rate have been observed in patients using DENLAZYD. DENLAZYD 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 have been observed. Measurement of serum lipids should be considered during treatment with DENLAZYD (see section 4.8).

Seizures

Cases of seizures were reported in premarketing clinical trials with desvenlafaxine. DENLAZYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from premarketing clinical trials. DENLAZYD should be prescribed with caution in patients with a seizure disorder (see section 4.8).

Discontinuation effects

During marketing of SNRIs and SSRIs, such as DENLAZYD, 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. paraesthesia 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 DENLAZYD. 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, DENLAZYD 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 DENLAZYD, 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 DENLAZYD) therapy have been reported. The possibility of these adverse events should be considered in patients treated with DENLAZYD who present with progressive dyspnoea, cough or chest discomfort. Such patients should undergo a prompt medical evaluation, and

discontinuation of DENLAZYD 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 DENLAZYD should be considered when determining dose (see sections 4.2 and 5.2).

No overall differences in safety or efficacy were observed between younger patients and patients 65 years of age or older. However, 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 DENLAZYD.

Paediatric population

Safety and efficacy in children under 18 years of age have 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 Interactions 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 DENLAZYD (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 DENLAZYD 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 DENLAZYD in combination with other CNS-active medicines has not been systematically evaluated. Consequently, caution is advised when DENLAZYD is taken in combination with other CNS-active medicines.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with DENLAZYD 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 DENLAZYD.

Potential for other medicines to affect DENLAZYD

Inhibitors of CYP3A4

CYP3A4 is involved in DENLAZYD elimination. Concomitant use of DENLAZYD with potent inhibitors of CYP3A4 may result in higher exposure to DENLAZYD.

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 DENLAZYD.

Potential for DENLAZYD to affect other medicines

Medicines metabolised by CYP2D6

Clinical trials have shown that desvenlafaxine is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. Concomitant use of DENLAZYD with a medicine metabolised by CYP2D6 may result in increased concentrations of that medicine and decreased concentrations of its CYP2D6 metabolites.

Medicines metabolised by CYP3A4

In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozymes. Concomitant use of DENLAZYD 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 desvenlafaxine (100 mg daily) does not have a clinically relevant effect on medicines metabolised by a combination of both CYP2D6 and CYP3A4 enzymes.

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

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

Laboratory test interactions

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

Electroconvulsive therapy

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

4.6 Fertility, pregnancy and lactation

Pregnancy

DENLAZYD must not be administered to pregnant women. Safety during pregnancy has not been established (see section 4.3).

If DENLAZYD 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

DENLAZYD must not be administered to lactating women. Safety during lactation has not been established (see section 4.3).

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

Fertility

No data on male or female fertility is available.

4.7 Effects on ability to drive and use machines

DENLAZYD may impair judgement, thinking and motor skills. Therefore, patients should be cautioned about their ability to drive a vehicle or operate hazardous machinery (see section 4.4).

4.8 Undesirable effects

Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Immune system disorders	Less frequent	Hypersensitivity.
Metabolism and nutritional 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.
Nervous system disorders	Frequent	Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention, vertigo.
	Less frequent	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.
	Frequency unknown	Acute pancreatitis.
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, rash.
	Less frequent	Alopecia, photosensitivity reaction, angioedema.
	Frequency unknown	Stevens-Johnson syndrome**.
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal stiffness.
Renal and urinary disorders	Frequent	Urinary hesitation, proteinuria, urinary retention.
Reproductive system and breast disorders	Frequent	Erectile dysfunction*, delayed ejaculation*, ejaculation failure*.
	Less frequent	Ejaculation disorder*, sexual dysfunction.
	Frequency unknown	Postpartum haemorrhage***.
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

* 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 sections 4.4 and 4.6).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DENLAZYD is important. It allows continued monitoring of the benefit/risk balance of DENLAZYD. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is limited clinical experience with desvenlafaxine overdosage in humans.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Other antidepressants.

ATC code: N06AX23.

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, H1-histaminergic or α1-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

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 oral administration. Area under the curve (AUC) and C_{max} of 6 747 ng•h/mL and 376 ng/mL, respectively, are predicted after a single dose of 100 mg.

Distribution

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.

Biotransformation

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.

Elimination

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.

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 were achieved within approximately 4 – 5 days. At steady state, multiple dose accumulation of desvenlafaxine is linear and predictable from the single dose pharmacokinetic profile.

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.

Effects of food

A food-effect trial involving administration of desvenlafaxine to healthy participants 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.

Special populations

Elderly patients

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 a 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), moderate (CrCl 30 – 50 mL/min), severe (CrCl < 30 mL/min) renal impairment end-stage renal disease (ESRD) (requiring dialysis) and to healthy, age-matched control subjects.

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 h 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), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment and in healthy subjects.

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 have not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Purified stearic acid

Talc

Xanthan gum.

Coating materials

Coating materials for DENLAZYD 50:

Opadry Pink [containing iron oxide red (E172), iron oxide yellow (E172), macrogol/PEG (E1521), polyvinyl alcohol partially hydrolysed (E1203), talc (E1521), titanium dioxide (E171)].

Coating materials for DENLAZYD 100:

Opadry Brown [containing iron oxide red E172, FD&C Yellow #6/Sunset Yellow FCF aluminium

lake (E110), macrogol/PEG (E1521), polyvinyl alcohol – partially hydrolysed (E1203), talc (E1521), titanium dioxide (E171)].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C in a dry place.

Protect from light.

6.5 Nature and contents of container

PVDC/PVC and aluminium blister strip containing 10 or 15 tablets packed into an outer carton.

Pack size: 30 tablets (3 strips of 10 tablets or 2 strips of 15).

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

DENLAZYD 50: 57/1.2/0461

DENLAZYD 100: 57/1.2/0462

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06 May 2025

10. DATE OF REVISION OF THE TEXT

Not applicable.