Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
VENLAFIX-100

2. Qualitative and quantitative composition
Each film coated extended release tablet contains Desvenlafaxine Succinate equivalent to Desvenlafaxine 100 mg

This product contains lactose.
For a full list of excipients, see section 6.1

3. Pharmaceutical form
Film coated extended Release Tablets 100 mg

Brown coloured round shaped biconvex both side plain film coated extended release tablets

4. Clinical particulars

4.1 Therapeutic indications
Desvenlafaxine succinate extended release tablet 100 mg, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).
The efficacy of Desvenlafaxine succinate extended release tablet 100 mg has been established in four 8-week, placebo-controlled studies of outpatients who met DSMIV criteria for major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

4.2 Posology and method of administration
Initial Treatment of Major Depressive Disorder The recommended dose for Desvenlafaxine succinate extended release tablet 100 mg is 100 mg once daily, with or without food. In clinical studies, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses. When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms
Desvenlafaxine succinate extended release tablet 100 mg should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Special Populations

Pregnant women during the third trimester

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with Desvenlafaxine succinate extended release tablet 100 mg during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Desvenlafaxine succinate extended release tablet 100 MG in the third trimester. Patients with renal impairment No dosage adjustment is necessary in patients with mild renal impairment (24-hr CrCl = 50 80 mL/min). The recommended dose in patients with moderate renal impairment (24-hr CrCl = 30 50 mL/min) is 50 mg per day. The recommended 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. Supplemental doses should not be given to patients after dialysis. The doses should not be escalated in patients with moderate or severe renal impairment, or ESRD [see Warnings and Precautions (5.10), Use in Specific Populations (8.6) and Clinical Pharmacology.

Patients with hepatic impairment

Dose escalation above 100 mg/day is not recommended

Elderly patients

No dosage adjustment is required solely on the basis of age; however, the possibility of reduced renal clearance of Desvenlafaxine succinate extended release tablet 100 mg should be considered when determining the dose.

4.3 Contraindications

Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Desvenlafaxine succinate extended release tablet 100 mg formulation listed in section 6.1.

Monoamine Oxidase Inhibitors

Desvenlafaxine succinate extended release tablet 100 mg must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Based on the half-life of desvenlafaxine, at least 7. days should be allowed after stopping Desvenlafaxine succinate extended release tablet 100 mg before starting an MAOI Dosage and Administration.

4.4 Special warnings and precautions for use

Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of shortterm placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depressionWorsening and Suicide Risk

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4.5 Interaction with other medicinal products and other forms of interaction

Central Nervous System (CNS)-Active Agents

The risk of using Desvenlafaxine succinate extended release tablet 100 mg in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when tablet is taken in combination with other CNSactive drugs.

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 Desvenlafaxine succinate extended release tablet 100 mg (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI.

Serotonergic Drugs

Based on the mechanism of action of Desvenlafaxine succinate extended release tablet 100 mg and the potential for serotonin syndrome, caution is advised when tablet is co-administered with other drugs that may affect the serotonergic neurotransmitter systems.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when tablet is initiated or discontinued.

Potential for Other Drugs to Affect Desvenlafaxine

Inhibitors of CYP3A4 (ketoconazole) CYP3A4 is a minor pathway for the metabolism of desvenlafaxine succinate extended release tablet 100 mg. In a clinical study, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine succinate extended release tablet 100 mg (400 mg single dose) by about 43% and Cmax by about 8%. Concomitant use of desvenlafaxine succinate extended release tablet 100 mg with potent inhibitors of CYP3A4 may result in higher concentrations of desvenlafaxine succinate extended release tablet 100 mg. Inhibitors of other CYP enzymes Based on in vitro data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine succinate extended release tablet 100 mg.

Potential for Desvenlafaxine to Affect Other Drugs

Drugs metabolized by CYP2D6 (desipramine) In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the Cmax and AUC of desipramine increased approximately 25% and 17%, respectively. When 400 mg (8 times the recommended 50 mg dose) was administered, the Cmax and AUC of desipramine increased approximately 50% and 90%, respectively. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam) In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. In a clinical study, desvenlafaxine succinate extended release tablet 100 mg daily (8 times the recommended 50 mg dose) was co-administered with a single 4 mg dose of midazolam (a CYP3A4 substrate). The AUC and Cmax of midazolam decreased by approximately 31% and 16%, respectively. Concomitant use of desvenlafaxine succinate extended release tablet 100 mg with a drug metabolized by CYP3A4 can result in lower exposures to that drug.

4.6 Pregnancy and Lactation

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Teratogenic effects – Pregnancy Category C When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 10 times a human dose of 100 mg/day (on a mg/m2 basis) in rats, and up to 15 times a human dose of 100 mg/day (on a mg/m2 basis) in rabbits. However, fetal weights were decreased in rats, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m2 basis). When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 10 times a human dose of 100 mg/day (on a mg/m2 basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 29 times a human dose of 100 mg/day (on a mg/m2 basis). There are no adequate and well-controlled studies of desvenlafaxine succinate extended release tablet 100 mg in pregnant women. Therefore, desvenlafaxine succinate extended release tablet 100 mg should be used during pregnancy only if the potential benefits justify the potential risks

Non-teratogenic effects Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. When treating a pregnant woman with desvenlafaxine succinate extended release tablet 100 mg during the third trimester, the physician should carefully consider the potential risks and benefits of treatment

4.7 Effects on ability to drive and use machines

Do not drive a car or operate machinery until you know how desvenlafaxine affects you.

4.8 Undesirable effects

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity
- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
- Serotonin Syndrome
- Elevated Blood Pressure
- Increased Risk of Bleeding
- Angle Closure Glaucoma
- Activation of Mania/ Hypomania
- Discontinuation Syndrome
- Seizure
- Hyponatremia
- Interstitial Lung Disease and Eosinophilic Pneumonia

<u>Common adverse reactions in placebo-controlled MDD studies</u>

The most commonly observed adverse reactions in desvenlafaxine treated MDD patients in premarketing pooled 8-week, placebo-controlled, fixed-dose studies (incidence ≥ 5% and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Other adverse reactions observed in premarketing and postmarketing clinical studies

Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of < 2% in MDD patients treated with desvenlafaxine extended-release tablets were:

Cardiac disorders: Tachycardia.

General disorders and administration site conditions: Asthenia.

Investigations: Weight increased, liver function test abnormal, blood prolactin increased.

Musculoskeletal and connective tissue disorders: Musculoskeletal stiffness.

Nervous system disorders: Syncope, convulsion, dystonia.

Psychiatric disorders: Depersonalization, bruxism.

Renal and urinary disorders: Urinary retention.

Skin and subcutaneous tissue disorders: Rash, alopecia, photosensitivity reaction, angioedema

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poison board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Desvenlafaxine overdose causes minor effects with mild hypertension and tachycardia. The risk of seizures or serotonin toxicity is low.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Desvenlafaxine lacked significant affinity for numerous receptors, including muscariniccholinergic, H1-histaminergic, or α1-adrenergic receptors in vitro. PRISTIQ also lacked monoamine oxidase (MAO) inhibitory activity.

5.2 Pharmacokinetic properties

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. The mean terminal half-life, t1/2, 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.

Absorption and Distribution:

The absolute oral bioavailability of desvenlafaxine after oral administration is about 80%. Mean time to peak plasma concentrations (Tmax) is about 7.5 hours after oral administration. A food-effect study involving administration of desvenlafaxine to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the Cmax was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, desvenlafaxine tablet can be taken without regard to meals. The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. The desvenlafaxine volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

Metabolism and Elimination

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and < 5% as the oxidative metabolite (N,Odidesmethylvenlafaxine) in urine.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

Desvenlafaxine succinate did not increase the incidence of tumours in long-term mouse and rat carcinogenicity studies at oral doses up to 7 (mice), 14 (male rats) and 23 (female rats) times the maximal recommended human dose of 200 mg/day, on a mg/m2 basis.

6. Pharmaceutical Particulars

6.1 List of Excipients

Hypromellose (RLQ 350)
Lactose Monohydrate
Isopropyl Alcohol
Sodium CMC
Talc
Magnesium Stearate
Povidone K-30

Hypromellose E 15
Titanium Dioxide
Colour Red Oxide Of Iron
Methylene Dichloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

3 years

6.4 Special Precautions for storage

Store at temperatures not exceeding 30 ^{0}C

6.5 Nature and Content of container

10 tablets pack in one Alu-Alu Blister. Such 3 Blister pack in carton along with insert.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. Marketing Authorization Holder

HIRAL LABS LTD

8. Marketing Authorization Number

CTD8769

9. Date of first authorization/renewal of the authorization

17/04/2023

10. Date of revision of the text

05/05/2025