PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Dexinor 50 XR 50 mg extended-release tablets

Dexinor 100 XR 100 mg extended-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dexinor 50 XR:

Each extended-release tablet contains desvenlafaxine benzoate equivalent to 50 mg desvenlafaxine.

Dexinor 100 XR:

Each extended-release tablet contains desvenlafaxine benzoate equivalent to 100 mg desvenlafaxine.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dexinor 50 XR:

Extended release tablets, light pink, biconvex, round shaped film coated tablets debossed with “DV” on one side and “50” on the other side.

Dexinor 100 XR:

Extended release tablets, reddish-orange, biconvex, round shaped film coated tablets, debossed with "DV" on one side and "100" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive disorder:

Dexinor XR 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 Dexinor XR 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 Dexinor XR:

Symptoms associated with discontinuation of Dexinor XR, other Serotonin-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 section 4.4 and section 4.8).

Switching patients from other antidepressants to Dexinor XR:

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to Dexinor XR. 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 Dexinor XR should be considered when determining dose (see section 5.2).

Paediatric population:

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

Method of administration

For oral use.

Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved (see section 4.4).

4.3 Contraindications

- Hypersensitivity to Dexinor XR, venlafaxine hydrochloride or to any excipients in the Dexinor XR formulation.
- Dexinor XR is an inhibitor of both norepinephrine and serotonin reuptake. Dexinor XR 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

Dexinor XR at least 7 days should be allowed after stopping Dexinor XR before starting an MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines such as Dexinor XR 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 section 4.4 and section 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 Dexinor XR 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.

Due to 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 Dexinor XR 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, Dexinor XR should be tapered (see section 4.2).

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:

Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. Patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Dexinor XR should be used cautiously in patients with a history or family history of mania or hypomania (see section 4.8).

Serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:

The development of a potentially life-threatening serotonin syndrome may occur with Dexinor XR treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs and triptans) and with medicines that impair metabolism of serotonin (including MAOIs) or with antipsychotics or other dopamine antagonists (see section 4.3).

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).

Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes (see section 4.5).

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

Treatment with Dexinor XR should be discontinued if serotonin syndrome or NMS-Like reactions occur and supportive symptomatic treatment initiated.

Narrow-angle glaucoma:

Mydriasis has been reported in association with Dexinor XR; 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 have been 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.

Discontinuation symptoms:

Adverse reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment include: dizziness, withdrawal syndrome, nausea headache, irritability, diarrhoea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation symptoms occurred more frequently with longer duration of therapy (see section 4.2).

Adverse reactions reported with other SNRIs:

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

Effects on activities requiring concentration and performance:

Interference with cognitive and motor performance:

There have been no reports of any 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 Dexinor XR therapy does not adversely affect their ability to engage in such activities.

Abuse and dependence:

Physical and psychological dependence:

There has been no indication of drug-seeking behaviour.

It is not possible to predict on the basis of pre-marketing data, the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of desvenlafaxine (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

Co-administration of medicines containing venlafaxine and/or Dexinor XR:

Desvenlafaxine is the major active metabolite of venlafaxine, a medication used to treat major depressive, generalised anxiety, social anxiety and panic disorders.

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

Effects on blood pressure:

Increased blood pressure:

Pre-existing hypertension should be controlled before treatment with Dexinor XR. Patients receiving Dexinor XR should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Dexinor XR. Sustained blood pressure increases could have adverse consequences.

For patients who experience a sustained increase in blood pressure while receiving Dexinor XR, 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 Geriatric use).

Cardiovascular/cerebrovascular:

Caution is advised in administering Desvenlafaxine to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Dexinor XR has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.

Serum lipids:

Measurement of serum lipids should be considered during treatment with Dexinor XR (see section 4.8).

Seizures:

Cases of seizures have been reported. Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Dexinor XR 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 such as Desvenlafaxine, 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 Dexinor XR. 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 section 4.2 and section 4.8).

Abnormal bleeding:

Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation. As with other agents that inhibit serotonin-reuptake, Dexinor XR should be used cautiously in patients predisposed to bleeding.

Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the risk. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Dexinor XR and NSAIDs, ASA, or other drugs that affect coagulation (see section 4.5). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g, thrombocytopenia).

Hyponatraemia:

Cases of hyponatraemia and/or the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) secretion have been described with SNRIs (including desvenlafaxine) and SSRIs, 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 Dexinor XR) therapy have been reported.

The possibility of these adverse events should be considered in patients treated with Dexinor XR who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Dexinor XR should be considered.

Sexual dysfunction:

SNRIs may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Special populations

Use in elderly patients

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of Dexinor XR should be considered when determining dose (see section 4.2 and section 5.2).

Greater sensitivity of some older individuals cannot be ruled out.

Paediatric population:

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

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 Dexinor XR (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 Dexinor XR in patients taking monoamine oxidase inhibitors (MAOIs), including selegiline and linezolid (an antibiotic which is a reversible non-selective MAOI) is contraindicated (see section 4.3 and section 4.4).

Central nervous system (CNS)-active agents:

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

Serotonin syndrome:

Serotonin syndrome, a potentially life-threatening condition, may occur with Dexinor XR treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, St. John's Wort [*Hypericum perforatum*], pethidine), with medicines that impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], (see 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).

If concomitant treatment with desvenlafaxine and other agents that may affect the serotonergic neurotransmitter system (such as an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist (triptan)) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

Ethanol:

Patients should be advised to avoid alcohol consumption while taking Dexinor XR.

Potential for other medicines to affect Dexinor XR

Inhibitors of CYP3A4:

CYP3A4 is involved in Dexinor XR elimination. Studies indicate that ketoconazole (200 mg twice daily) increased the area under the concentration vs. time curve (AUC) of desvenlafaxine, (400 mg single dose) by approximately 43 %, a weak interaction and Cmax by about 8 %. Concomitant use of Dexinor XR with potent inhibitors of CYP3A4 may result in higher exposure to Dexinor XR.

Inhibitors of other CYP enzymes:

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 desvenlafaxine.

Potential for Dexinor XR to affect other medicines:

Medicines metabolised by CYP2D6:

Studies have shown that desvenlafaxine is a weak inhibitor of CYP2D6 at a dose of 100 mg daily. When desvenlafaxine 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 desvenlafaxine 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 Dexinor XR 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. In studies when Desvenlafaxine 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 in which desvenlafaxine 50 mg daily was co-administered with a single 4 mg dose of midazolam, the AUC and Cmax of midazolam decreased by approximately 29 % and 14 % respectively.

Concomitant use of Dexinor XR 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):

Dexinor XR (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, Dexinor XR 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, Dexinor XR 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 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 Dexinor XR therapy.

Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish Dexinor XR from PCP and amphetamine.

Electroconvulsive therapy:

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

4.6 Fertility, pregnancy and lactation

Dexinor XR 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 Dexinor XR in human pregnancy has not been established. If Dexinor XR 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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the new born (PPHN). This potential risk cannot be ruled out with desvenlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

Breastfeeding

Dexinor XR (O-desmethylvenlafaxine) is excreted in human milk.

Because of the potential for serious adverse reactions in nursing infants from Dexinor XR, a decision should be made whether or not to discontinue nursing or to discontinue Dexinor XR, taking into account the importance of the medicine to the mother.

Fertility

There is no information available on fertility with Dexinor XR.

4.7 Effects on ability to drive and use machines

Dexinor XR 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

Summary of the safety profile

(See section 4.4)

Tabulated list of adverse reactions

System Organ Class	Frequency	Side effect
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, abnormal orgasm, withdrawal syndrome
	Less frequent	Depersonalisation, hypomania, hallucinations mania
Nervous system disorders	Frequent	Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention
	Less frequent	Syncope, extrapyramidal disorder, dyskinesia, convulsion, dystonia, serotonin syndrome
Eye disorders	Frequent	Blurred vision, mydriasis

System Organ Class	Frequency	Side effect
Ear and labyrinth disorders	Frequent	Tinnitus, vertigo
Cardiac disorders	Frequent	Palpitations, tachycardia
	Less frequent	Stress cardiomyopathy (Takotsubo cardiomyopathy)
Vascular disorders	Frequent	Hot flush, blood pressure increased
	Less frequent	Orthostatic hypotension (see section 4.4), peripheral coldness
Respiratory, thoracic and mediastinal disorders	Frequent	Yawning
	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Nausea, dry mouth, constipation, diarrhoea, vomiting
	Less frequent	Acute pancreatitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhidrosis, rash
	Less frequent	Alopecia, photosensitivity reaction, angioedema, Stevens-Johnson syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent	Musculoskeletal stiffness
Renal and urinary disorders	Frequent	Urinary hesitation
	Less frequent	Proteinuria, urinary retention
Reproductive system and breast disorders	Frequent	Erectile dysfunction, delayed ejaculation, ejaculation failure, ejaculation disorder
	Less frequent	Sexual dysfunction

System Organ Class	Frequency	Side effect
General disorders and administration site conditions	Frequent	Fatigue, chills, asthenia, feeling jittery, irritability
Investigations	Frequent	Increased weight, increased blood pressure, decreased weight, blood cholesterol increased, abnormal liver function test
	Less frequent	Increased blood triglycerides, increased blood prolactin

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Side effects must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za.

4.9 Overdose

There is limited experience with Dexinor XR overdosage in humans.

No specific antidotes for Dexinor XR 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. Activated charcoal should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

ATC code: N06AX23

Non-clinical studies have shown that desvenlafaxine 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 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.

Administration with food has minimal impact on drug absorption. Following administration with low, medium, and high-fat meals, increases in C_{max} of approximately 16 % (observed confidence interval: 107,8-125,1 %; required confidence interval for bioequivalence 80-125 %) were observed only following a high-fat meal.

The plasma protein binding of desvenlafaxine is low (30 %) and is independent of drug concentration. Desvenlafaxine's volume of distribution at steady-state following intravenous administration is 3,4 l/kg, indicating distribution into nonvascular compartments.

Metabolism and elimination:

Approximately 45 % of desvenlafaxine is excreted unchanged in urine.

Desvenlafaxine is primarily metabolised by conjugation (mediated by UGT isoforms, including UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) and to a minor extent through oxidative metabolism. Approximately 19 % of the administered dose is excreted as the glucuronide metabolite and < 5 % as the oxidative metabolite (N, O-didesmethylvenlafaxine) in urine. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

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:

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).

Paediatric:

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

Patients with renal impairment:

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:

No dosage adjustment is necessary for patients with hepatic impairment.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline

Colloidal silicone dioxide

Hypromellose

Opadry pink 85F94487 (50 mg only)

Opadry pink 85F94527 (100 mg only)

Stearic acid

Talc

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

Dexinor 50 XR and Dexinor 100 XR are packed in blisters using Clear PVC/ Aclar & Aluminium foil lidding.

Dexinor XR tablets are available in pack sizes of 30’s.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Streets

Woodstock, Cape Town, 8001

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8 REGISTRATION NUMBERS

Dexinor 50 XR: 56/1.2/0735

Dexinor 100 XR: 56/1.2/0736

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 May 2025

10 DATE OF REVISION OF THE TEXT

Not applicable