1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VOLOXIN 50 mg (extended release tablet).

VOLOXIN 100 mg (extended release tablet).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each extended release tablet of VOLOXIN 100 mg contains desvenlafaxine succinate equivalent to 100 mg desvenlafaxine.

For full list of excipients, see section 6.1.

Sugar free

3. PHARMACEUTICAL FORM

Extended release tablet.

VOLOXIN 50 mg

Light pink coloured, round, biconvex, film coated tablets, debossed with ‘50’ on one side and plain on other side

VOLOXIN 100 mg

Dark brown to red coloured, round, biconvex, film coated tablets, debossed with ‘100’ on one side and plain on other side

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VOLOXIN is indicated for the treatment of major depressive disorder (MDD).

4.2. Posology and method of administration

Posology

Major depressive disorder

The recommended dose for VOLOXIN 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.

Use in patients with renal impairment

The recommended starting dose in patients with severe renal impairment (24-hour CrCl < 30ml/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).

Paediatric use

Safety and efficacy in patients less than 18 years of age has not been established (see section 4.3).

Use in elderly patients

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

Discontinuing VOLOXIN

Symptoms associated with discontinuation of VOLOXIN, as well as other serotonin and noradrenalin 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).

Switching patients from other antidepressants to VOLOXIN

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

Method of administration

For oral use.

It is recommended that VOLOXIN extended release tablets are taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

4.3. Contraindications

VOLOXIN is contraindicated in:

- Patients with hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in VOLOXIN (see section 6.1).
- Concomitant use with monoamine oxidase inhibitors (MAOI), including linezolid or methylene blue, or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of VOLOXIN, at least 7 days should be allowed after stopping VOLOXIN

before starting a MAOI. Severe adverse reactions have been reported when therapy is initiated with SSRI/SNRI medicines such as VOLOXIN soon after discontinuation of a 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 4.4 and 4.5)

- In patients less than 18 years of age as the safety and efficacy has not been established (see section 4.4).
- 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 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 VOLOXIN should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic

regimen, including possibly discontinuing VOLOXIN in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder, 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.

If the decision is made to discontinue treatment, VOLOXIN should be tapered (see section 4.2).

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 age 65 years and older.

There have been reports of hostility, suicidal ideation and self-harm with use of SSRIs in children under the age of 18 years.

Mania/hypomania

Mania has been reported for 0,03 % of patients treated with desvenlafaxine, as in VOLOXIN. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. VOLOXIN should be used cautiously in patients with a history or family history of mania or hypomania (see section 4.8).

Screening patients for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder.

Prior to initiating treatment with an antidepressant, including VOLOXIN, 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. It should be noted that VOLOXIN is not approved for use in treating bipolar depression.

Serotonin syndrome

The development of a potentially life-threatening serotonin syndrome may occur with VOLOXIN treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St. John's Wort) and with medicines that impair metabolism of serotonin (including MAOIs intended to treat psychiatric disorders and also others, such as linezolid and methylene blue). Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, delirium and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing and hyperthermia), neuromuscular aberrations (e.g. tremor, rigidity, myoclonus, hyperreflexia and incoordination) seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhoea) (see section 4.6). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of VOLOXIN with MAOIs intended to treat psychiatric disorders or others such as linezolid and methylene blue, is contraindicated. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking VOLOXIN. VOLOXIN should be discontinued before initiating treatment with the MAOI (see section 4.3).

Narrow-angle glaucoma

Mydriasis has been reported in association with desvenlafaxine, as in VOLOXIN; 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 reports of ischaemic cardiac adverse events, including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine, as in VOLOXIN treatment as compared to placebo.

Discontinuation symptoms and effects

Adverse reactions reported in ≥ 2 % of patients in association with abrupt discontinuation, dose reduction or tapering of treatment include: dizziness, withdrawal syndrome, nausea and

headache. In general, discontinuation symptoms occurs more frequently with longer duration of therapy (see section 4.2).

There have also been reports of adverse events occurring upon discontinuation of SNRIs and SSRIs, 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 VOLOXIN. 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 4.8).

Adverse reactions leading to discontinuation of therapy

The most common adverse reaction leading to discontinuation in at least 2 % of patients treated with desvenlafaxine, as in VOLOXIN in the first 12 weeks of treatment is nausea (see section 4.8).

Adverse reactions reported with other SNRIs

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

Interference with cognitive and motor performance

The behavioural performance of healthy individuals taking desvenlafaxine, as in VOLOXIN, revealed no clinically significant impairment of psychomotor, cognitive, or complex behaviour performance. However, since any CNS-active medicine may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that VOLOXIN therapy does not adversely affect their ability to engage in such activities.

Physical and psychological dependence

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

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

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

Increased blood pressure

Increases in blood pressure have been documented in some patients receiving desvenlafaxine, as in VOLOXIN, particularly with higher doses. Pre-existing hypertension should be controlled before initiating treatment with VOLOXIN. Patients receiving VOLOXIN should have regular monitoring of blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine, as in VOLOXIN. Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving VOLOXIN, 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/lipid metabolism disorders

Caution is advised in administering VOLOXIN to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and heart rate have been documented with desvenlafaxine, as in VOLOXIN. VOLOXIN has not been systematically evaluated in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease (see section 4.8).

Serum lipids

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were documented in patients receiving desvenlafaxine, as in

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

Seizures

Cases of seizures have been reported with desvenlafaxine, as in VOLOXIN. VOLOXIN has not been systematically evaluated in patients with a seizure disorder. VOLOXIN should be prescribed with caution in patients with a seizure disorder (see section 4.8).

Abnormal bleeding

SSRIs and SNRIs, including VOLOXIN, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Medicines that inhibit serotonin uptake in platelets may lead to abnormalities of platelet aggregation. Data has demonstrated an association between use of medicine that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening haemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of VOLOXIN and NSAIDs, aspirin, or other medicines that affect coagulation or bleeding. As with other medicines that inhibit serotonin-reuptake, VOLOXIN 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 VOLOXIN, usually in volume-depleted or dehydrated patients, including elderly patients and patients taking diuretics (see section 4.8).

Discontinuation of VOLOXIN should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Interstitial lung disease and eosinophilic pneumonia

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

Use in the elderly

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of VOLOXIN should be considered when determining dose (see section 4.2 and 5). No overall differences in safety or efficacy have been documented between patients over the age of 65 and younger patients; however, there is a higher incidence of systolic orthostatic hypotension in patients treated with VOLOXIN who are ≥ 65 years of age compared to patients < 65 years of age. In addition, there may be increases in systolic blood pressure in patients ≥ 65 years of age compared to patients < 65 years of age treated with VOLOXIN.

Paediatric use

Safety and efficacy in children under 18 years of age has not been established (see section 4.3 and 4.8). Increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm have been reported with SSRI and SNRI use in major depressive disorder (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

Adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on antidepressants with pharmacological properties similar to desvenlafaxine, as in VOLOXIN, (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 VOLOXIN in patients taking MAOIs is contraindicated (see section 4.2, 4.3 and 4.4).

Central nervous system (CNS)-active medicines

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

Serotonergic medicines

Based on the pharmacokinetic mechanism of action of desvenlafaxine, as in VOLOXIN, and the potential for serotonin syndrome, caution is advised when VOLOXIN is co-administered with other medicines that may affect the serotonergic neurotransmitter systems (see section 4.3 and 4.4).

Serotonin syndrome, a potentially life-threatening condition, may occur with VOLOXIN 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)), 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 4.3 and 4.4).

Medicines that interfere with haemostasis (NSAIDs, aspirin, and warfarin)

Serotonin release by platelets plays an important role in haemostasis. An association between use of psychotropic medicines that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding has been demonstrated. Concurrent use of a NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VOLOXIN is initiated or discontinued (see section 4.4).

Potential for other medicines to affect VOLOXIN

Inhibitors of CYP3A4

CYP3A4 is involved in VOLOXIN elimination (see section 5). Concomitant use of VOLOXIN with potent inhibitors of CYP3A4 may result in higher exposure to VOLOXIN.

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 VOLOXIN (see section 5).

Potential for VOLOXIN to affect other medicines

Medicines metabolised by CYP2D6

Desvenlafaxine, as in VOLOXIN, is a weak inhibitor of CYP2D6 when dosed at a 100 mg daily. Concomitant use of VOLOXIN with a medicine (e.g. desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine) metabolised by CYP2D6 may result in increased concentrations of that medicine and decreased concentrations of its CYP2D6 metabolites. Substrates primarily metabolised by CYP2D6 should be dosed at the original level when co-administered with VOLOXIN 100 mg or lower.

Medicines metabolised by CYP3A4

Desvenlafaxine, as in VOLOXIN does not inhibit or induce the CYP3A4 isozymes (e.g. midazolam). Concomitant use of VOLOXIN 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)

Desvenlafaxine, as in VOLOXIN (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

Desvenlafaxine, as in VOLOXIN, 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 (see section 5).

P-glycoprotein transporter

Desvenlafaxine, as in VOLOXIN, is not a substrate or an inhibitor for the P-glycoprotein transporter.

Other medicines containing desvenlafaxine or venlafaxine

Use of VOLOXIN with other desvenlafaxine or venlafaxine containing medicines should be avoided. The concomitant use of VOLOXIN with other desvenlafaxine or venlafaxine containing medicines will increase desvenlafaxine blood levels and increase dose-related adverse reactions (see section 4.4 and 4.8).

Ethanol

Patients should be advised to avoid alcohol consumption while taking VOLOXIN.

Laboratory test interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking VOLOXIN. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of VOLOXIN therapy.

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

Electroconvulsive therapy

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

4.6. Fertility, pregnancy and lactation

VOLOXIN is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

The safety of VOLOXIN in human pregnancy has not been established. If VOLOXIN 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 or later. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, 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 4.4). Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Lactation

Desvenlafaxine, as in VOLOXIN is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from VOLOXIN, a decision should be made whether to discontinue nursing or to discontinue VOLOXIN, taking into account the importance of the treatment to the mother.

4.7. Effects on ability to drive and use machines

Since adverse reactions such as dizziness, somnolence, disturbance in attention and blurred vision have been reported in patients receiving VOLOXIN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that VOLOXIN does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a. Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Immune system disorders		Hypersensitivity, angioedema	
Metabolism and nutrition disorders	Decreased appetite	Hyponatraemia	
Psychiatric disorders	Insomnia, anxiety, abnormal dreams, nervousness, decreased libido,	Withdrawal syndrome, abnormal orgasm, depersonalisation, hypomania, hallucinations,	

	anorgasmia	bruxism	
Nervous system disorders	Dizziness, headache, somnolence, tremor, paraesthesia, dysgeusia, disturbance in attention, vertigo	Syncope, convulsion, dystonia	
Eye disorders	Blurred vision, mydriasis		
Ear and labyrinth disorders	Tinnitus		
Cardiac disorders	Palpitations, tachycardia	Myocardial ischemia, myocardial infarction, coronary occlusion requiring revascularisation	
Vascular disorders	Hot flush	Orthostatic hypotension, peripheral coldness, hypertension	
Respiratory, thoracic and mediastinal disorders	Yawning	Epistaxis	
Gastrointestinal disorders	Nausea, dry mouth, constipation, diarrhoea, vomiting		Acute pancreatitis
Skin and subcutaneous tissue disorders	Hyperhidrosis, rash	Alopecia, photosensitivity reaction	Stevens-Johnson syndrome
Musculoskeletal, connective tissue and bone disorders	Musculo-skeletal stiffness		
Renal and urinary disorders		Urinary hesitation, urinary retention	
Reproductive system and breast disorders	Erectile dysfunction, delayed ejaculation, ejaculation failure	Ejaculation disorder, sexual dysfunction	
General disorders and administrative site conditions	Fatigue, chills, asthenia, feeling jittery, irritability		
Investigations	Increased weight, increased blood pressure, decreased weight	Increased blood cholesterol, increased blood triglycerides, abnormal liver function test, increased blood prolactin, proteinuria	

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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/

Aspen Pharmacare:
E-mail: Drugsafety@aspenpharma.com
Tel: 0800 118 088

4.9. Overdose

Symptoms

There is limited experience with VOLOXIN overdosage in humans. However, desvenlafaxine, as in VOLOXIN, is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent medicine of desvenlafaxine) is presented below.

The most commonly reported events in overdosage with venlafaxine include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Treatment

No specific antidotes for VOLOXIN 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

Pharmacotherapeutic group: Other antidepressants – ATC code NO6AX23

Mechanism of action

Desvenlafaxine succinate is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The efficacy of desvenlafaxine in the treatment of major depressive disorder (MDD) 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 a study desvenlafaxine also lacks significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacks monoamine oxidase inhibitory activity. In addition, desvenlafaxine lacks significant activity in the 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. AUC and C_{max} of 6 747 ng.hour/mL and 376 ng/mL, respectively, are predicted after a single dose of 100 mg. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days.

The C_{max} of desvenlafaxine is increased about 16 % in the fed state (high-fat meal), while the AUCs are similar between the fed and fasting state. This difference is not clinically significant; therefore, desvenlafaxine can be taken without regard to meals.

Distribution

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

Biotransformation

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. CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Elimination

The mean terminal half-life, $t_{1/2}$ is approximately 11 hours. Approximately 45 % of desvenlafaxine is excreted unchanged in urine. Approximately 19 % of the administered 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. At steady state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

Special Populations

Gender

There is a statistically significant increase in exposure in females compared to males (C_{max} 18 % to 37 % greater; AUC 6 % to 17 % greater).

Renal impairment

The pharmacokinetics of a single dose of desvenlafaxine succinate 100 mg as contained in VOLOXIN were studied in subjects with mild (CrCl 50 to 80 ml/min) (n=9), moderate (CrCl 30 to 50 ml/min) (n=8), severe (CrCl < 30 mL/min) (n=7), end-stage renal disease (ESRD) (n=9) requiring dialysis and to healthy, age-matched control subjects (n=8). Elimination was significantly correlated with creatinine clearance. Total body clearance was reduced by 29 % in

mild, 39 % in moderate, 51 % in severe renal impairment, and 58 % in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42 % in mild, 56 % in moderate, 108 % in severe (24-hr CrCl < 30 ml/min), and 116 % in ESRD subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11,1 hours in the healthy subjects to 13,5, 15,5, 17,6 and 22,8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively.

Less than 5 % of the medicine in the body was cleared during a standard 4-hour haemodialysis procedure.

Supplemental doses should not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant impairment of renal function (see section 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of desvenlafaxine succinate 100 mg were studied in subjects with mild (ChildPugh A, n=8), moderate (Child-Pugh B, n=8), and severe (Child-Pugh C, n=8) hepatic impairment and in healthy subjects (n=12).

Average AUC was increased by approximately 31 % and 35 % in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were comparable in subjects with mild hepatic impairment and healthy subjects (< 5 % difference).

Systemic clearance (CL/F) was decreased by approximately 20 % and 36 % in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5 % difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively (see section 4.2).

No dosage adjustment is necessary for patients with hepatic impairment (see section 4.2).

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.

Elderly patients

In a trial of healthy subjects administered doses up to 300 mg of desvenlafaxine as contained in VOLOXIN, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32 % increase in C_{max} and a 55 % increase in AUC values in subjects greater than 75 years of age, as compared with subjects 18 to 45 years of age.

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see section 4.2 and 4.4).

Paediatric patients

Safety and efficacy in patients less than 18 years of age has not been established (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose, iron oxide (E172), macrogol, magnesium stearate, microcrystalline cellulose, povidone, talc, titanium dioxide (E171).

Sugar free.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 30 °C.

Protect from moisture.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

7, 14 or 28 tablets are packed in silver aluminium/aluminium foil blisters. Blister strips are packed in an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

VOLOXIN 50 mg: 52/1.2/0952

VOLOXIN 100 mg: 52/1.2/0953

9. DATE OF FIRST AUTHORISATION

05 May 2020

10. DATE OF REVISION OF TEXT

05 May 2020

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