Professional Information for VOXBRINT

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VOXBRINT 5 film-coated tablets

VOXBRINT 10 film-coated tablets

VOXBRINT 20 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VOXBRINT 5: Each film-coated tablet contains 5 mg vortioxetine (as vortioxetine hydrobromide).

VOXBRINT 10: Each film-coated tablet contains 10 mg vortioxetine (as vortioxetine hydrobromide).

VOXBRINT 20: Each film-coated tablet contains 20 mg vortioxetine (as vortioxetine hydrobromide).

Contains sugar alcohol:

VOXBRINT 5 contains 11,25 mg mannitol per tablet.

VOXBRINT 10 contains 22,5 mg mannitol per tablet.

VOXBRINT 20 contains 45,0 mg mannitol per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VOXBRINT 5: White coloured, round shaped, biconvex, film-coated tablets debossed with "V" on one side and "5" on other side.

VOXBRINT 10: White coloured, almond shaped, biconvex, film-coated tablets debossed with "V" on one side and "10" on other side.

VOXBRINT 20: White coloured, almond shaped, biconvex, film-coated tablets debossed with "V" on one side and "20" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VOXBRINT is indicated for the treatment of major depressive disorder episodes and to reduce the risk of relapse.

4.2 Posology and method of administration

Posology

VOXBRINT is for oral use in adults.

The starting and recommended dose is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily, or reduced to a minimum of 5 mg daily. If a dose increase is required, this should be in periods of not less than one week of the treatment. A dose decrease may be considered for patients who do not tolerate higher doses.

After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response. Patients can abruptly stop taking VOXBRINT without the need for a gradual reduction in dose.

Special populations

Elderly patients

The safety and efficacy of VOXBRINT have been established in elderly patients. However, caution should be exercised when treating these patients. Treatment should be initiated with 5 mg daily and, depending on the individual patient response, the dose may be increased to 10 mg daily. Data on doses exceeding 10 mg daily in the elderly are limited (see sections 4.4 and 5.2).

Renal or hepatic impairment

No dose adjustment is needed based on renal or hepatic function (see sections 4.4 and 5.2).

Cytochrome P450 (CYP450) inhibitors

Depending on individual response, a lower dose of VOXBRINT may be considered if strong CYP2D6 inhibitors (such as bupropion, quinidine, fluoxetine, paroxetine) are added to VOXBRINT treatment (see section 4.5).

Cytochrome P450 inducers

Depending on individual patient response, a dose adjustment of VOXBRINT may be considered if a broad CYP450 inducer (such as rifampicin, carbamazepine, phenytoin) is added to VOXBRINT treatment (see section 4.5).

Paediatric patients

The safety and efficacy of VOXBRINT in children and adolescents aged less than 18 years have not been established (see section 4.4). No data are available.

Method of administration

VOXBRINT is for oral use.

VOXBRINT can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to vortioxetine or to any of the excipients of VOXBRINT listed in section 6.1.
- Concomitant use with monoamine oxidase inhibitors (MAOIs) including linezolid (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population

The safety and efficacy of vortioxetine have not been established in patients under 18 years of age and the treatment of depression with VOXBRINT is therefore not recommended in this age group (see section 4.2). Clinical studies in children and adolescents treated with other antidepressants indicated that suicide-related behaviour (such as suicide attempt and suicidal thoughts) and

hostility (predominantly aggression, oppositional behaviour and anger) are more frequently observed in these children than in those treated with a placebo.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events), which persists until significant remission occurs. Improvement may not be present during the initial few weeks or more of treatment with VOXBRINT and patients should therefore be closely monitored until such improvement arises. General clinical experience demonstrates that the risk of suicide may increase in the initial stages of recovery.

Patients are known to be at greater risk of suicidal thoughts or suicidal attempts when they present with a history of suicide-related events or displayed a significant degree of suicidal ideation prior to commencement of treatment. These patients should receive careful monitoring during treatment. When compared to placebo, an increased risk of suicidal behaviour with antidepressants was showed by a meta-analysis of placebo-controlled clinical studies of antidepressants in adult patients with psychiatric disorders and under the age of 25 years old.

Treatment with VOXBRINT needs to be accompanied by close supervision of the patient, particularly those at high risk, in early treatment and following dose adjustments. The patients (as well as their caregivers) must be informed of the necessity to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek immediate medical advice if these symptoms present.

Seizures

There is a potential risk of seizures with the use of antidepressants such as VOXBRINT. In patients with a history of seizures or unstable epilepsy, VOXBRINT should therefore be introduced with caution (see section 4.5). Treatment should be terminated in any patient who develops seizures or for whom an increase in the frequency of seizures occurs.

Serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS)

Serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS) are potentially life-threatening conditions and may occur with VOXBRINT. An increased risk for SS or NMS results from the concurrent use of VOXBRINT and serotonergic-active substances (including triptans), medicines that impair the metabolism of serotonin (including MAOIs), antipsychotic medicines and other dopamine antagonists. Monitoring of patients for the development of signs and symptoms of SS or NMS is advised (see sections 4.3 and 4.5).

The symptoms of SS may include mental status changes (such as agitation, hallucinations, coma), autonomic instability (such as tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (such as hyperreflexia, uncoordination) and/or gastrointestinal symptoms (such as nausea, vomiting, diarrhoea). If this occurs, treatment with VOXBRINT should be discontinued immediately and symptomatic treatment should be initiated.

Hyponatraemia

There have been reports of hyponatraemia, most likely due to inappropriate antidiuretic hormone secretion, with the use of antidepressants with serotonergic effect (SSRIs and SNRIs). Caution is therefore advised in patients at risk, such as the elderly, patients with liver cirrhosis or patients concomitantly treated with medicines known to cause hyponatraemia. Discontinuation of VOXBRINT should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Mania/hypomania

Caution is advised with VOXBRINT in patients with a history of mania or hypomania. The treatment should be discontinued in any patient entering a manic phase.

Aggression/agitation

Patients treated with antidepressants, including vortioxetine, may also experience feelings of

aggression, anger, agitation and irritability. Patient's condition and disease status should be closely monitored. Patients (and caregivers of patients) should be alerted to seek medical advice, if aggressive/agitated behaviour emerges or aggravates.

Haemorrhage

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events, such as gastrointestinal or gynaecological bleeding with the use of antidepressants with serotonergic effect, such as VOXBRINT. Caution is advised with VOXBRINT in patients receiving anticoagulant treatment or other medicines known to exert an effect on platelet function (such as atypical antipsychotics and phenothiazines, most tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin) (see section 4.5). Caution is also advised in patients with known bleeding disorders or tendencies.

Co-administration with cytochrome P450 inhibitors

Co-administration of VOXBRINT and bupropion resulted in a higher incidence of adverse reactions when bupropion was added to VOXBRINT than when VOXBRINT was added to bupropion. Depending on individual patient response, a lower dose of VOXBRINT may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VOXBRINT treatment (see sections 4.2 and 4.5).

Glaucoma

Mydriasis has been reported in association with use of antidepressants, including vortioxetine. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma. Caution is advised when prescribing VOXBRINT to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Elderly patients

Caution is advised when treating elderly patients with doses higher than 10 mg once daily, as data

on the use of VOXBRINT in elderly patients with major depressive episodes are limited (see sections 4.2, 4.8 and 5.2).

Renal impairment or hepatic impairment

Given that patients with renal or hepatic impairment are vulnerable and that the data on the use of VOXBRINT in these subpopulations are limited, caution should be exercised when treating these patients (see sections 4.2 and 5.2).

4.5 Interaction with other medicines and other forms of interaction

Vortioxetine is extensively metabolised in the liver primarily through oxidation and subsequent glucuronic acid conjugation. *In vitro,* the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine (see section 5.2).

Monoamine oxidase inhibitors (MAOIs)

Due to the risk of serotonin syndrome, VOXBRINT is contraindicated in any combination with monoamine oxidase inhibitors (MAOIs) (see section 4.3). Following the discontinuation of treatment with a MAOI, a waiting period of at least 14 days is required before treatment with VOXBRINT can be initiated. VOXBRINT must be discontinued for at least 14 days before treatment with an irreversible nonselective MAOI can be initiated.

Linezolid

The antibiotic linezolid is a weak MAOI and should not be given to patients treated with VOXBRINT. Close monitoring for serotonin syndrome is necessary if used concomitantly (see section 4.4).

Serotonergic medicines

Serotonin syndrome may result from the co-administration of VOXBRINT and medicines with

serotonergic effect, such as pethidine, tramadol, sumatriptan and other triptans (see section 4.4).

St. John's wort

Concomitant use of antidepressants with serotonergic effect and herbal medicines containing St. John's wort (*Hypericum perforatum*) may result in a higher incidence of adverse reactions, including serotonin syndrome (see section 4.4).

Medicines lowering the seizure threshold

The threshold for seizures can be lowered by antidepressants with serotonergic effect such as VOXBRINT. Caution is therefore advised in the co-administration of VOXBRINT and other medicines capable of lowering the seizure threshold, such as antidepressants (tricyclic antidepressants, SSRIs and SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol (see section 4.4).

Electroconvulsive therapy (ECT)

Caution is advised in patients receiving ECT, as there is no clinical experience with the concurrent administration of VOXBRINT and ECT.

CYP2D6 inhibitors

Following the co-administration of vortioxetine 10 mg daily and bupropion (a strong CYP2D6 inhibitor) 150 mg twice daily in healthy subjects for 14 days, the exposure to vortioxetine increased 2,3-fold for area under the curve (AUC). A higher incidence of adverse events resulted from bupropion being added to vortioxetine therapy, than when vortioxetine was added to bupropion therapy. If a strong CYP2D6 inhibitor (such as bupropion, quinidine, fluoxetine, paroxetine) is added to VOXBRINT treatment, a lower dose of VOXBRINT may be considered depending on individual patient response (see section 4.2).

CYP3A4, CYP2C9, and CYP2C19 inhibitors

When vortioxetine was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) or following 6 days of fluconazole 200 mg/day (a CYP3A4/5, CYP2C9 and CYP2C19 inhibitor) in healthy subjects, a 1,3-fold and 1,5-fold increase, respectively, in vortioxetine AUC was observed. No dose adjustment is required when co-administering VOXBRINT with a CYP3A4/5, CYP2C9 or CYP2C19 inhibitor.

No inhibitory effect of 40 mg single-dose omeprazole (CYP2C19 inhibitor) was observed on the multiple-dose pharmacokinetics of vortioxetine in healthy subjects.

Interactions in CYP2D6 poor metabolisers

Co-administration of strong inhibitors of CYP3A4 (such as itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, conivaptan and many of the HIV protease inhibitors) and inhibitors of CYP2C9 (such as fluconazole and amiodarone) to CYP2D6 poor metabolisers (see section 5.2) has not been investigated specifically, but it is anticipated that it will lead to a more marked increased exposure of vortioxetine in these patients as compared to the moderate effect described above. Depending on individual patient response, a lower dose of VOXBRINT may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in CYP2D6 poor metabolisers.

Cytochrome P450 inducers

When a single dose of 20 mg vortioxetine was co-administered following 10 days of rifampicin 600 mg/day (a broad inducer of CYP isozymes) in healthy subjects, a 72% decrease in AUC of vortioxetine was observed. Depending on individual patient response, a dose adjustment may be considered if a broad cytochrome P450 inducer (such as rifampicin, carbamazepine, phenytoin) is added to VOXBRINT treatment (see section 4.2).

Alcohol

Studies showed that following the co-administration of a single dose of 20 mg or 40 mg vortioxetine with a single dose of ethanol (0,6 g/kg) in healthy subjects, no effect on the pharmacokinetics of vortioxetine or ethanol were observed. When compared to the placebo, no significant impairment of cognitive function was observed. The intake of alcohol during VOXBRINT treatment is however not advised.

Aspirin

In pharmacokinetic studies, no effect on the multiple-dose pharmacokinetics of vortioxetine was observed in healthy subjects following the administration of multiple doses of aspirin (150 mg/day) (see section 4.4).

The effects VOXBRINT on other medicine

Anticoagulants and antiplatelet medicines

No significant effects, relative to placebo, were observed in international normalised ratio (INR), prothrombin or plasma R-/S-warfarin values following co-administration of multiple doses of vortioxetine with stable doses of warfarin in healthy subjects. Also, no significant inhibitory effect, relative to placebo, on platelet aggregation or pharmacokinetics of acetylsalicylic acid or salicylic acid was observed when aspirin 150 mg/day was co-administered following multiple doses of vortioxetine administration in healthy subjects. However, caution should be exercised when VOXBRINT is combined with oral anticoagulants or antiplatelet medicines due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see section 4.4).

Cytochrome P450 substrates

According to *in vitro* studies, VOXBRINT does not have any relevant potential to inhibit or induce cytochrome P450 isozymes (see section 5.2). Studies indicate no inhibitory effect on the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinyl estradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or

CYP2D6 (dextromethorphan) following the administration of multiple doses of vortioxetine in healthy subjects.

No pharmacodynamic interactions were observed. No significant impairment, relative to placebo, in cognitive function was observed for vortioxetine following co-administration with a single 10 mg dose of diazepam. No significant effects, relative to placebo, were observed in the levels of sex hormones following co-administration of vortioxetine with a combined oral contraceptive (ethinyl estradiol 30 µg/ levonorgestrel 150 µg).

Lithium, tryptophan

Following the co-administration of lithium with multiple doses of vortioxetine in healthy subjects, an absence of clinically relevant effect was found during steady-state lithium exposure. There have however been reports of an increase in effects following the concomitant use of lithium or tryptophan and antidepressants with serotonergic effect. Caution is advised with the concomitant use of VOXBRINT and lithium or tryptophan.

Interference with urine drug screens

There have been reports of false positive results in urine enzyme immunoassays for methadone in patients who have taken vortioxetine. Caution should be exercised in the interpretation of positive urine drug screen results, and confirmation by an alternative analytical technique (e.g. chromatographic methods) should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

VOXBRINT should not be taken during pregnancy or by women with child-bearing potential not using contraception. Safety and efficacy in pregnant women have not been established.
Studies in animals have indicated reproductive toxicity.

The following symptoms may occur in the newborn after maternal use of a serotonergic medicine in the later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In the majority of instances, such complications began immediately or soon (< 24 hours) after delivery.

Data from epidemiological studies propose an increased risk of persistent pulmonary hypertension in the newborn (PPHN) when SSRIs are used in pregnancy, particularly in late pregnancy. The association of PPHN with VOXBRINT have not been studied and the potential risk should therefore not be neglected, considering the related mechanism of action of VOXBRINT (increase in serotonin concentrations).

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action (see section 4.4).

Breastfeeding

Mothers should not breastfeed their infants when taking VOXBRINT. The safety of VOXBRINT in breastfeeding women has not been established. Vortioxetine and/or its metabolites are excreted into the milk of lactating rats.

Fertility

Fertility studies in male and female rats showed no effect of vortioxetine on fertility, sperm quality or mating performance.

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

Side effects such as dizziness may occur and impair the ability to drive or operate machines. Caution is advised before driving a vehicle or operating machinery until the effects of VOXBRINT are known, particularly at the start of treatment or following a dose adjustment.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction was nausea. The adverse reactions usually occur within the first two weeks of treatment.

The following undesirable effects have been reported during clinical trials and post-marketing experience with vortioxetine

Immune system disorders

Frequency unknown: anaphylactic reaction*, angioedema*

Endocrine disorders

Frequency unknown: hyperprolactinaemia*

Metabolism and nutrition disorders

Frequency unknown: hyponatraemia*

Psychiatric disorders

Frequent: abnormal dreams

Frequency unknown: insomnia*, agitation*, aggression* (see section 4.4 for aggression and agitation).

Nervous system disorders

Frequent:	dizziness
Frequency unknown:	serotonin syndrome*, headache*

Eye disorders

Less frequent:	mydriasis (which may lead to acute narrow angle glaucoma – see section 4.4)

Vascular disorders

Less frequent:	flushing
Frequency unknown:	haemorrhage* (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)

Gastrointestinal disorders

Frequent:	nausea, diarrhoea, constipation, vomiting

Skin and subcutaneous tissue disorders

Frequent:	pruritis (including generalised pruritis), hyperhidrosis
Less frequent:	night sweats
Frequency unknown:	urticaria*, rash*

* Based on post-marketing experience.

Description of selected adverse reactions

Nausea

Nausea was usually mild or moderate and occurred within the first two weeks of treatment. The reactions were usually transient and did not generally lead to cessation of therapy. Gastrointestinal adverse reactions, such as nausea, occurred more frequently in women than men.

Elderly patients

For doses ≥ 10 mg vortioxetine once daily, the withdrawal rate from the studies was higher in patients aged ≥ 65 years.

For doses of 20 mg vortioxetine once daily, the incidences of nausea and constipation were higher in patients aged ≥ 65 years than in patients aged < 65 years (see section 4.4).

Sexual dysfunction

When using the Arizona sexual experience scale (ASEX) to assess sexual dysfunction, clinical studies found that doses of 5 – 15 mg vortioxetine did not result in any difference when compared to placebo. An increase in sexual dysfunction (including difficulties with satisfaction of orgasm and ease of sexual arousal) was however seen following a dose of 20 mg vortioxetine (see section 5.1).

Class effect

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving a medicine from related pharmacological classes of antidepressants (SSRIs or TCAs). The mechanism behind this risk is unknown, and it is not known if this risk is also relevant for vortioxetine as in VOXBRINT.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VOXBRINT is important. It allows continued monitoring of the benefit/risk balance of VOXBRINT. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose

Ingestion of vortioxetine in clinical trials in the dose range of 40 mg to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience with vortioxetine is associated with overdoses of up to 80 mg and for most cases, no or mild symptoms were reported. Nausea and vomiting were the most frequently reported symptoms.

Experience with vortioxetine overdose in doses higher than 80 mg is limited. Reports of serotonin syndrome and events of seizures followed dosages several fold higher than the therapeutic dose range.

Management of overdose

In the event of an overdose, symptomatic measures should be employed and patients should be monitored as appropriate. It is advised that patients be medically followed-up in a specialised environment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants

ATC code: N06AX26.

Mechanism of action

It is thought that the mechanism of action of vortioxetine is associated with its multimodal activity, which is direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Data resulting from non-clinical studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and

5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin but probably also the norepinephrine (noradrenaline), dopamine, histamine, acetylcholine, gamma butyric acid (GABA) and glutamate systems in the forebrain.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, vortioxetine is slowly, but well absorbed and reaches peak plasma concentration (C_{max}) within 7 – 11 hours. When multiple doses of 5, 10 or 20 mg/day were administered, mean C_{max} values of 9 – 33 ng/mL were observed. The absolute bioavailability is 75 % and concomitant food administration has no effect on the pharmacokinetics of vortioxetine. (see section 4.2).

Distribution

Vortioxetine is highly bound to plasma proteins (98 – 99 %) and protein binding appears to be independent of vortioxetine plasma concentrations. The mean volume of distribution (V_{ss}) of vortioxetine is 2 600 L, indicating widespread extravascular distribution.

Biotransformation

Vortioxetine undergoes extensive hepatic metabolism, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9, and subsequent glucuronic acid conjugation. The main vortioxetine metabolite is pharmacologically inactive. *In vitro*, the CYP 450 isozymes CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine.

During interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5, vortioxetine had no inhibitory or inducing effects on these isozymes (see section 4.5). Vortioxetine is a poor P-glycoprotein substrate and inhibitor.

Elimination

Vortioxetine has a mean elimination half-life of 66 hours and the oral clearance is 33 L/h. Steady-state plasma concentrations are achieved in approximately 2 weeks. Vortioxetine metabolites are excreted in both the urine (approximately 2/3) and faeces (approximately 1/3). Only negligible amounts of vortioxetine are excreted in the faeces.

Linearity/non-linearity

The pharmacokinetics were observed to be linear and time independent in a studied dose range of 2,5 to 60 mg/day. In compliance with the half-life,
the accumulation index is 5 – 6 based on AUC_{0-24h} following multiple doses of 5 – 20 mg/day.

Special populations

Elderly

Following multiple doses of 10 mg per day, the exposure to vortioxetine increased up to 27 % (C_{max} and AUC) in healthy subjects aged 65 years and older, in comparison to younger healthy subjects aged 45 years and older. When treating elderly patients (≥ 65 years), the starting dose should always be the lowest effective dose of 5 mg vortioxetine once daily (see section 4.2). Caution is advised when prescribing doses higher than 10 mg vortioxetine once daily to elderly patients (see section 4.4).

Renal impairment

The administration of single doses of 10 mg vortioxetine in patients with mild, moderate and severe renal impairment (estimated using the Cockcroft-Gault formula) resulted in modest exposure increases (up to 30 %), compared to healthy controls. Following a single 10 mg dose of vortioxetine in patients with end-stage renal disease, only a small fraction was lost during dialysis, as the AUC and C_{max} were 13 % and 27 % lower, respectively. No dose adjustment is therefore needed in patients with renal impairment (see section 4.4).

Hepatic impairment

The pharmacokinetics in subjects (N = 6 – 8) with mild, moderate, or severe hepatic impairment (Child-Pugh Criteria A, B, or C, respectively) were compared to healthy volunteers. The changes in AUC were less than 10 % lower in subjects with mild or moderate hepatic impairment, and 10 % higher in those with severe hepatic impairment. The changes in Cmax were less than 25 % lower in all groups. No dose adjustment is needed based on hepatic function (see Section 4.2 and 4.4)

CYP2D6 gene types

When compared to extensive metabolisers, the vortioxetine plasma concentration was approximately two times higher in CYP2D6 poor metabolisers. The concomitant use of strong CYP3A4/2C9 inhibitors and vortioxetine in CYP2D6 poor metabolisers could potentially result in higher exposure (see section 4.5).

In CYP2D6 ultra-rapid metabolisers, the plasma concentration of vortioxetine 10 mg/day were between those obtained in extensive metabolisers at 5 mg/day and 10 mg/day. A dose adjustment may therefore be considered, depending on individual patient response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Hydroxypropyl cellulose (E 463)

Magnesium stearate

Mannitol (E421)

Microcrystalline cellulose (E460)

Sodium starch glycolate.

Film coating:

Opadry White (containing hypromellose (E464), macrogol (E1521) and titanium dioxide (E171)).

6.2 Incompatibilities

None.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear transparent PVC/PVdC and aluminium foil blister strips with 10 or 14 film-coated tablets, packed in an outer cardboard container.

Pack size: 10, 14, 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

VOXBRINT 5: 55/1.2/0600

VOXBRINT 10: 55/1.2/0601

VOXBRINT 20: 55/1.2/0602

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2023

10. DATE OF REVISION OF THE TEXT

12 February 2025