SCHEDULING STATUS
S5

1. NAME OF THE MEDICINE

VORTIOXETINE 5 mg LUNDBECK film-coated tablets

VORTIOXETINE 10 mg LUNDBECK film-coated tablets

VORTIOXETINE 15 mg LUNDBECK film-coated tablets

VORTIOXETINE 20 mg LUNDBECK film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VORTIOXETINE 5 mg LUNDBECK tablet contains vortioxetine hydrobromide equivalent to 5 mg vortioxetine.

Each VORTIOXETINE 10 mg LUNDBECK tablet contains vortioxetine hydrobromide equivalent to 10 mg vortioxetine.

Each VORTIOXETINE 15 mg LUNDBECK tablet contains vortioxetine hydrobromide equivalent to 15 mg vortioxetine.

Each VORTIOXETINE 20 mg LUNDBECK tablet contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

3. PHARMACEUTICAL FORM

5 mg: Pink, almond-shaped film-coated tablet engraved with “TL” on one side and “5” on the other side.

10 mg: Yellow, almond-shaped film-coated tablet engraved with “TL” on one side and “10” on the other side.

15 mg: Orange, almond-shaped film-coated tablet engraved with “TL” on one side and “15” on the other side.

20 mg: Red, almond-shaped film-coated tablet engraved with “TL” on one side and “20” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VORTIOXETINE LUNDBECK is indicated for the treatment of major depressive disorder and to reduce the risk of relapse.

4.2 Posology and method of administration

VORTIOXETINE LUNDBECK is for oral use in adults.

The starting and recommended dose of VORTIOXETINE LUNDBECK 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. VORTIOXETINE LUNDBECK can be taken without regard to meals.

After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

Patients being treated with VORTIOXETINE LUNDBECK can abruptly stop taking VORTIOXETINE LUNDBECK without the need for a gradual reduction in dose.

Elderly patients

The safety and efficacy of VORTIOXETINE LUNDBECK have been established in elderly patients. However, caution should be exercised when treating the elderly. Treatment should be initiated with 5 mg daily and, depending on the individual patient response, the dose may be increased to 10 mg daily. Limited data are available with doses exceeding 10 mg daily.

Paediatric patients

The safety and efficacy of VORTIOXETINE LUNDBECK in children and adolescents aged less than 18 years have not been established. No data are available.

Renal impairment

No dose adjustment is needed for patients with renal impairment or for patients with end-stage renal disease. However, caution should be exercised when treating patients with severe renal insufficiency (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. VORTIOXETINE LUNDBECK has not been studied in patients with severe hepatic impairment

and caution should be exercised when prescribing to these patients (see Section 5.2 Pharmacokinetic properties).

Cytochrome P450 inhibitors

Depending on individual patient response, a lower dose of VORTIOXETINE LUNDBECK may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE LUNDBECK treatment (see Section 4.5 Interaction with other medicines and other forms of interaction).

Cytochrome P450 inducers

Depending on individual patient response, a dose adjustment of VORTIOXETINE LUNDBECK may be considered if a broad cytochrome P450 inducer (e.g. rifampicin, carbamazepine, phenytoin) is added to VORTIOXETINE LUNDBECK treatment (see Section 4.5 Interaction with other medicines and other forms of interaction).

4.3 Contraindications

Hypersensitivity to vortioxetine or to any of the excipients of VORTIOXETINE LUNDBECK.

Concomitant use of VORTIOXETINE LUNDBECK with monoamine oxidase inhibitors (MAOIs) (see Section 4.5 Interaction with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use

Use in paediatric population

VORTIOXETINE LUNDBECK is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of VORTIOXETINE LUNDBECK have not been established in this age group (see Section 4.2 Posology and method of administration). In clinical studies in children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed than in those treated with placebo.

Suicide, suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment with VORTIOXETINE LUNDBECK,

patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment with VORTIOXETINE LUNDBECK. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany treatment with VORTIOXETINE LUNDBECK especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Seizures

Seizures are a potential risk with antidepressants, including VORTIOXETINE LUNDBECK. Therefore, VORTIOXETINE LUNDBECK should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment with VORTIOXETINE LUNDBECK should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.

Serotonin syndrome or neuroleptic malignant syndrome

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS), potentially life threatening conditions, may occur with VORTIOXETINE LUNDBECK. The risk of SS or NMS is increased with concomitant use of serotonergic medicines (including triptans), with medicines which impair metabolism of serotonin (including MAOIs), antipsychotics and other dopamine antagonists. Patients should be monitored for the emergence of signs and symptoms of SS or NMS (see Section 4.3 Contraindications and Section 4.5 Interaction with other medicines and other forms of interaction).

Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). If this occurs, treatment with VORTIOXETINE LUNDBECK should be discontinued immediately and symptomatic treatment should be initiated.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of antidepressants with serotonergic effect (SSRIs/SNRIs). Caution should be exercised in patients at risk, such as the elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.
Discontinuation of VORTIOXETINE LUNDBECK should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Activation of hypomania or mania

VORTIOXETINE LUNDBECK treatment should be used with caution in patients with a history of mania/hypomania, and should be discontinued in any patient entering a manic phase.

Haemorrhage

Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events such as gastrointestinal or gynaecological bleeding may occur with VORTIOXETINE LUNDBECK. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (see Section 4.5 Interaction with other medicines and other forms of interaction), and in patients with known bleeding tendencies/disorders.

Co-administration with cytochrome P450 inhibitors

Co-administration of VORTIOXETINE LUNDBECK and bupropion resulted in a higher incidence of adverse reactions when bupropion was added to VORTIOXETINE LUNDBECK than when VORTIOXETINE LUNDBECK was added to bupropion. Depending on individual patient response, a lower dose of VORTIOXETINE LUNDBECK may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE LUNDBECK treatment (see Section 4.2 Posology and method of administration and Section 4.5 Interaction with other medicines and other forms of interaction).

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 Pharmacokinetic properties).

Monoamine Oxidase Inhibitors (MAOIs)

Due to the risk of serotonin syndrome, VORTIOXETINE LUNDBECK is contraindicated in any combination with MAOIs. VORTIOXETINE LUNDBECK must not be initiated for at least 14 days after discontinuation of treatment with an MAOI. VORTIOXETINE LUNDBECK must be discontinued for at least 14 days before starting treatment with an MAOI (see Section 4.3 Contraindications).

Linezolid

The antibiotic linezolid is a weak MAOI and should not be given to patients treated with VORTIOXETINE LUNDBECK. Close monitoring for serotonin syndrome is necessary if used concomitantly (see Section 4.4 Warnings and special precautions for use).

Serotonergic medicines

Co-administration of antidepressants with medicines with a serotonergic effect (e.g. pethidine, tramadol, sumatriptan and other triptans) may lead to serotonin syndrome (see Section 4.4 Warnings and special precautions for use).

St. John's Wort

Concomitant use of antidepressants with serotonergic effect, and herbal remedies containing St. John´s Wort (*Hypericum perforatum*) may result in a higher incidence of adverse reactions including serotonin syndrome (see Section 4.4 Warnings and special precautions for use).

Medicines lowering the seizure threshold

Antidepressants with serotonergic effect including VORTIOXETINE LUNDBECK can lower the seizure threshold. Caution is advised when concomitantly using VORTIOXETINE LUNDBECK and other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol) (see Section 4.4 Warnings and special precautions for use).

ECT (electroconvulsive therapy)

There is no clinical experience with concurrent administration of VORTIOXETINE LUNDBECK and ECT, therefore caution is advisable.

Cytochrome P450 inhibitors

The exposure to vortioxetine increased 2,3-fold for AUC when VORTIOXETINE LUNDBECK 10 mg/day was co-administered with bupropion (a strong CYP2D6 inhibitor) 150 mg twice daily for 14 days in 44 healthy subjects. The co-administration resulted in a higher incidence of adverse reactions when bupropion was added to VORTIOXETINE LUNDBECK than when

VORTIOXETINE LUNDBECK was added to bupropion. Depending on individual patient response, a lower dose of VORTIOXETINE LUNDBECK may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE LUNDBECK treatment (see Section 4.2 Posology and method of administration).

When VORTIOXETINE LUNDBECK 10 mg/day was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) in 17 healthy subjects, a 1,3-fold increase in vortioxetine AUC was observed. No dose adjustment is needed.

When VORTIOXETINE LUNDBECK 10 mg/day was co-administered following 6 days of fluconazole 200 mg/day (a CYP2C9, CYP2C19 and CYP3A4/5 inhibitor) in 16 healthy subjects, a 1,5-fold increase in AUC was observed. No dose adjustment is needed.

No inhibitory effect of 40 mg single dose omeprazole (CYP2C19 inhibitor) was observed on the multiple dose pharmacokinetics of VORTIOXETINE LUNDBECK (10 mg/day) in 15 healthy subjects.

Cytochrome P450 inducers

When a single dose of VORTIOXETINE LUNDBECK 20 mg was co-administered following 10 days of rifampicin 600 mg/day (a broad inducer of CYP isozymes) in 14 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 (e.g. rifampicin, carbamazepine, phenytoin) is added to VORTIOXETINE LUNDBECK treatment (see Section 4.2 Posology and method of administration).

Aspirin

No effect of multiple doses of aspirin 150 mg/day on multiple dose pharmacokinetics of VORTIOXETINE LUNDBECK 10 mg/day was observed in 28 healthy subjects.

Anticoagulants and antiplatelet medicines

No significant effects, relative to placebo, were observed in INR, prothrombin or plasma R-/S-warfarin values following co-administration of VORTIOXETINE LUNDBECK 10 mg/day for 14 days with stable doses of warfarin in 52 healthy subjects. Also, no significant inhibitory effect, relative to placebo, on platelet aggregation was observed when aspirin 150 mg/day was co-administered following 14 days of VORTIOXETINE LUNDBECK 10 mg/day administration in 28 healthy subjects. However, caution should be exercised when VORTIOXETINE LUNDBECK is combined with oral anticoagulants or antiplatelet medicinal products due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see Section 4.4 Warnings and special precautions for use).

Alcohol

No significant additional impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for VORTIOXETINE LUNDBECK single doses of 20 and 40 mg following co-administration with a single dose of ethanol 0,6 g/kg in 55 healthy subjects. However, the combination with alcohol is not advisable.

Diazepam

No significant impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for VORTIOXETINE LUNDBECK following co-administration of VORTIOXETINE LUNDBECK 10 mg/day with a single 10 mg dose of diazepam in 32 healthy subjects.

Oral contraceptives

No significant effects, relative to placebo, were observed in the levels of sex hormones following co-administration of VORTIOXETINE LUNDBECK 10 mg/day with a combined oral contraceptive (ethinyl estradiol 30 μg/ levonorgestrel 150 μg) in 25 healthy women for 21 days.

Cytochrome P450 substrates

In vitro, vortioxetine did not show any relevant potential for inhibition or induction of cytochrome P450 isozymes (see Section 5.2 Pharmacokinetic properties).

No inhibitory effect of VORTIOXETINE LUNDBECK (10 mg/day for 14 days) was observed in healthy subjects for the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP2C9 (warfarin), CYP3A4/5 (ethinyl estradiol), or CYP2B6 (bupropion). In a medicine interaction study in healthy subjects, no inhibitory effect of VORTIOXETINE LUNDBECK 10 mg/day for 14 days was observed for CYP2C9 (tolbutamide), CYP1A2 (caffeine), CYP3A4/5 (midazolam), or CYP2D6 (dextromethorphan).

Lithium, tryptophan

No clinically relevant effect was observed during steady-state lithium exposure following co-administration with VORTIOXETINE LUNDBECK 10 mg/day for 14 days in 16 healthy subjects. However, there have been reports of enhanced effects when antidepressants with serotonergic effect such as VORTIOXETINE LUNDBECK have been given together with lithium or tryptophan, therefore concomitant use of VORTIOXETINE LUNDBECK with these medicinal products should be undertaken with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

VORTIOXETINE LUNDBECK 's safety and efficacy in pregnant women has not been established.

The following symptoms may occur in the newborn after maternal use of VORTIOXETINE LUNDBECK in 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 a majority of instances, such complications begin immediately or soon (< 24 hours) after delivery.

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 newborn (PPHN). Although no studies have investigated the association of PPHN to VORTIOXETINE LUNDBECK treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Breastfeeding

The safety of VORTIOXETINE LUNDBECK in breastfeeding women has not been established. Vortioxetine and/or its metabolites are excreted into the milk of lactating rats.

4.7 Effects on ability to drive and use machines

As adverse reactions such as dizziness have been reported, patients should exercise caution when driving or operating hazardous machinery, especially when starting treatment with VORTIOXETINE LUNDBECK or when changing the dose.

4.8 Undesirable effects

The most common adverse reaction was nausea.

Table 1 enumerates the incidence of treatment emergent adverse events that occurred in the short-term placebo-controlled studies. Events included are those occurring in 1 % or more of patients treated with VORTIOXETINE LUNDBECK (5 to 20 mg/day), and for which the incidence in patients treated with VORTIOXETINE LUNDBECK was greater than the incidence in placebo-treated patients.

Table 1 Incidence of common adverse events for major depressive disorder, pool of 12

short-term studies

Body System / Adverse Event	Percentage of Patients Reporting				
	VORTIOXETINE LUNDBECK **5 mg/day (n=1157)**	VORTIOXETINE LUNDBECK **10 mg/day (n=1042)**	VORTIOXETINE LUNDBECK **15 mg/day (n=449)**	VORTIOXETINE LUNDBECK **20 mg/day (n=812)**	**Placebo (n=1968)**
Gastrointestinal Disorders					
Nausea	20,5*	22,6*	31,2*	27,2*	8,1
Diarrhoea	6,6	5,4	9,4*	5,5	5,5
Dry mouth	6,4	5,5	6,0	6,5	5,6
Constipation	3,4	3,6	5,6*	4,4*	2,9
Vomiting	2,7*	3,6*	6,5*	4,4*	1,1
Dyspepsia	1,8	1,7	2,4	2,1	1,9
Flatulence	1,0	1,9	2,0	0,9	1,2
Abdominal discomfort	1,4	0,6	2,0	1,6	1,1
General Disorders and Administration Site Conditions					
Fatigue	3,1	2,8	3,6	2,6	2,7
Infections and Infestations					
Naso-pharyngitis	5,3	4,0	3,6	4,9	3,9
Influenza	1,5	1,6	0,9	0,4	1,1
Injury, poisoning and procedural complications					
Accidental overdose	1,3	1,2	1,3	0,9	1,0
Metabolism and Nutrition Disorders					
Decreased appetite	2,1*	0,7	0,7	1,6	1,0
Musculoskeletal and Connective Tissue Disorders					
Back Pain	2,2	2,1	1,8	1,1	1,8
Arthralgia	0,9	0,9	1,8	1,1	0,9
Nervous System					
Headache	13,7	12,7	14,7	12,4	12,9
Dizziness	5,5	5,2	7,1	6,3	5,3
Somnolence	3,3	2,9	2,7	3,3	2,3
Sedation	1,2	0,5	1,3	1,5*	0,6
Psychiatric Disorders					
Insomnia	3,1	2,6	1,8	2,7	2,5
Skin and Subcutaneous Tissue Disorders					
Hyper-hidrosis	2,3	2,3	1,8	0,7	1,7
Pruritus generalised	0,4	1,3*	1,6*	1,8*	0,4

* Adverse events for which the difference to placebo is statistically significant (p<0.05)

Adverse reactions are listed below in Table 2 using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data). The table

includes all relevant side effects which occurred more frequently with VORTIOXETINE LUNDBECK treatment than with placebo treatment in clinical trials and post-marketing experience.

Table 2 Frequencies of adverse reactions

SYSTEM ORGAN CLASS	***FREQUENCY***	***ADVERSE REACTION***
Immune system disorders	*Not known**	Anaphylactic reaction
Metabolism and nutrition disorders	*Not known**	Hyponatraemia
Psychiatric disorders	*Common*	Abnormal dreams
Nervous system disorders	*Common*	Dizziness
	*Not known**	Serotonin syndrome
Vascular disorders	*Uncommon*	Flushing
	*Not known**	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	*Very common*	Nausea
	Common	Diarrhoea Constipation Vomiting
Skin and subcutaneous tissue disorders	*Common*	Pruritus, including generalised pruritis
	Uncommon	Night sweats
	*Not known**	Angioedema, urticaria, rash

*Based on post-marketing cases

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.

Sexual Dysfunction

VORTIOXETINE LUNDBECK may cause sexual dysfunction especially at the 20 mg dose. The following manifestations, i.e. difficulties with *satisfaction of orgasm* and *ease of sexual arousal,* as measured using the Arizona Sexual Experience Scale (ASEX), were the most prevalent for VORTIOXETINE LUNDBECK.

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 and TCAs). The mechanism behind this risk is unknown, and it is not known to what extent this risk is also relevant for VORTIOXETINE LUNDBECK.

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 asked to report any suspected adverse reactions to the South African Health Product Regulatory Authority (SAHPRA) via the '6.04 Adverse Drug Reactions Form' found online under SAHPRA's publications https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In clinical studies, no patient ingested more than 75 mg VORTIOXETINE LUNDBECK on a single occasion.

The clinical studies included subjects who were administered 40 to 75 mg. Ingestion of VORTIOXETINE LUNDBECK in this dose range caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience mainly concerns VORTIOXETINE LUNDBECK overdoses of up to 80 mg. The most frequently reported symptoms were nausea and vomiting.

There is limited experience with VORTIOXETINE LUNDBECK overdoses above 80 mg. Following dosages several fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported.

Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class

A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

The mechanism of action of vortioxetine is thought to be related to its multimodal activity, which is a combination of modulation of receptor activity and inhibition of the serotonin (5-HT) transporter. *In vitro* 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. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear. However, data from non-clinical 5-HT receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies suggest that the targets interact in a complex fashion, leading to modulation of neurotransmission in several systems, including serotonin, norepinephrine (noradrenaline), dopamine, histamine, acetylcholine, gamma butyric acid (GABA) and glutamate systems within the forebrain.

5.2 Pharmacokinetic properties

Absorption

Vortioxetine is slowly, but well absorbed after oral administration and the peak plasma concentration is reached within 7 to 11 hours. Following multiple dosing of 5, 10, or 20 mg/day, mean C_{max} values of 9 to 33 ng/ml were observed. The absolute bioavailability is 75 %. No effect of food on the pharmacokinetics was observed (see Section 4.2 Posology and method of administration).

Distribution

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

Biotransformation

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.

No inhibitory or inducing effect of vortioxetine was observed *in vitro* for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5. Vortioxetine is a poor P-gp substrate and inhibitor.

The major metabolite of vortioxetine is pharmacologically inactive.

Elimination

The mean elimination half-life and oral clearance are 66 hours and 33 ℓ/h, respectively. Approximately 2/3 of inactive vortioxetine metabolites are excreted in the urine and approximately 1/3 in the faeces. Only negligible amounts of vortioxetine are excreted in the faeces unchanged. Steady-state plasma concentrations are achieved in approximately 2 weeks.

Linearity/non-linearity

The pharmacokinetics are linear and time independent in the dose range studied (2,5 to 60 mg/day). In accordance with the half-life, the accumulation index is 5 to 6 based on $AUC_{0\text{-}24h}$ following multiple doses of 5 to 20 mg/day.

Pharmacokinetic/pharmacodynamic relationship

There is a curve-linear concentration-response relationship between the plasma concentrations of vortioxetine after single and multiple doses of 2,5 to 60 mg/day and the occupancy of the 5-HT transporter in the brain, as measured using PET.

Special patient populations

Elderly

In elderly healthy subjects (aged ≥ 65 years; n=20), the exposure to vortioxetine increased up to 27 % (C_{max} and AUC) compared to young healthy control subjects (aged ≤ 45 years) after multiple doses of 10 mg/day. Caution should therefore be exercised when treating the elderly (see Section 4.2 Posology and method of administration).

Renal impairment

Following a single dose of 10 mg vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, or severe; n=8 per group) caused modest exposure increases (up to 30 %), compared to healthy matched controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during dialysis (AUC and C_{max} were 13 % and 27 % lower; n=8) following a single 10 mg dose of vortioxetine. No dose adjustment is needed (see Section 4.2 Posology and method of administration).

Hepatic impairment

Following a single dose of 10 mg vortioxetine, no impact of mild or moderate hepatic impairment (Child-Pugh Criteria A or B; n=8 per group) was observed on the pharmacokinetics of vortioxetine (changes in AUC were less than 10%). No dose adjustment is needed. Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients (see Section 4.2 Posology and method of administration).

CYP2D6 poor metabolisers

The plasma concentrations of vortioxetine were approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. Depending on the individual patient response, a dose adjustment may be considered.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Hydroxypropylcellulose, mannitol, magnesium stearate, microcystalline cellulose, sodium starch glycolate (type A).

Tablet coating: Hypromellose, Macrogol 400, titanium dioxide (E171), iron oxide red (E172) (5, 15 and 20 mg tablets), iron oxide yellow (E172) (10 and 15 mg tablets).

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

VORTIOXETINE 5/10/15/20 mg LUNDBECK film-coated tablets are presented in transparent, colourless PVC/PVdC/aluminium blister packaging.

The blister cards are packed in an outer cardboard carton containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

H. Lundbeck (Pty) Ltd

Unit 9 Blueberry Office Park

Apple Street

Randpark Ridge Ext 114

2156

South Africa

8. REGISTRATION NUMBERS

5 mg: 55/1.2/0580

10 mg: 55/1.2/0581

15 mg: 55/1.2/0582

20 mg: 55/1.2/0583

9. DATE OF FIRST AUTHORISATION

15 March 2022

10. DATE OF REVISION OF THE TEXT