SCHEDULING STATUS
S5

1. NAME OF THE MEDICINE

BRINTELLIX 5 mg film-coated tablets

BRINTELLIX 10 mg film-coated tablets

BRINTELLIX 15 mg film-coated tablets

BRINTELLIX 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BRINTELLIX 5 mg tablet contains vortioxetine hydrobromide equivalent to 5 mg vortioxetine.

Each BRINTELLIX 10 mg tablet contains vortioxetine hydrobromide equivalent to 10 mg vortioxetine.

Each BRINTELLIX 15 mg tablet contains vortioxetine hydrobromide equivalent to 15 mg vortioxetine.

Each BRINTELLIX 20 mg tablet contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

For full list of excipients, see section 6.1

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

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

4.2 Posology and method of administration

Posology

BRINTELLIX is for oral use in adults.

The starting and recommended dose of BRINTELLIX 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. BRINTELLIX 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 BRINTELLIX can abruptly stop taking BRINTELLIX without the need for a gradual reduction in dose.

Special populations

Elderly patients

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

Renal or hepatic impairment

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

Cytochrome P450 inhibitors

Depending on individual patient response, a lower dose of BRINTELLIX may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to BRINTELLIX treatment (see Section 4.5).

Cytochrome P450 inducers

Depending on individual patient response, a dose adjustment of BRINTELLIX may be considered if a broad cytochrome P450 inducer (e.g. rifampicin, carbamazepine, phenytoin) is added to BRINTELLIX treatment (see Section 4.5).

Method of administration

BRINTELLIX is for oral use.

The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to vortioxetine or to any of the excipients of BRINTELLIX.

Concomitant use of BRINTELLIX with monoamine oxidase inhibitors (MAOIs) (see Section 4.5).

4.4 Special warnings and precautions for use

Use in paediatric population

BRINTELLIX is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of BRINTELLIX have not been established in this age group (see Section 4.2). 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 BRINTELLIX, 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 BRINTELLIX. 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 BRINTELLIX 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 BRINTELLIX. Therefore, BRINTELLIX should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment with BRINTELLIX 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 BRINTELLIX. 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 and Section 4.5).

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 BRINTELLIX 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 BRINTELLIX should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Activation of hypomania or mania

BRINTELLIX 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 BRINTELLIX. 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), and in patients with known bleeding tendencies/disorders.

Co-administration with cytochrome P450 inhibitors

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

Renal or hepatic impairment

Given that subjects with renal or hepatic impairment are vulnerable and given that the data on the use of BRINTELLIX in these subpopulations are limited, caution should be exercised when treating these patients (see Section 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, BRINTELLIX is contraindicated in any combination with MAOIs. BRINTELLIX must not be initiated for at least 14 days after discontinuation of treatment with an MAOI. BRINTELLIX must be discontinued for at least 14 days before starting treatment with an MAOI (see Section 4.3).

Linezolid

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

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).

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).

Medicines lowering the seizure threshold

Antidepressants with serotonergic effect including BRINTELLIX can lower the seizure threshold. Caution is advised when concomitantly using BRINTELLIX 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).

ECT (electroconvulsive therapy)

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

Cytochrome P450 inhibitors

The exposure to vortioxetine increased 2,3-fold for AUC when BRINTELLIX 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 BRINTELLIX than when BRINTELLIX was added to bupropion. Depending on individual patient response, a lower dose of BRINTELLIX may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to BRINTELLIX treatment (see Section 4.2).

When BRINTELLIX 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 BRINTELLIX 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 BRINTELLIX (10 mg/day) in 15 healthy subjects.

Cytochrome P450 inducers

When a single dose of BRINTELLIX 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 BRINTELLIX treatment (see Section 4.2).

Aspirin

No effect of multiple doses of aspirin 150 mg/day on multiple dose pharmacokinetics of BRINTELLIX 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 BRINTELLIX 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 BRINTELLIX 10 mg/day administration in 28 healthy subjects. However, caution should be exercised when BRINTELLIX 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).

Alcohol

No significant additional impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for BRINTELLIX 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 BRINTELLIX following co-administration of BRINTELLIX 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 BRINTELLIX 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).

No inhibitory effect of BRINTELLIX (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 BRINTELLIX 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 BRINTELLIX 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 BRINTELLIX have been given together with lithium or tryptophan, therefore concomitant use of BRINTELLIX with these medicinal products should be undertaken with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

BRINTELLIX should not be taken during pregnancy or by women with child-bearing potential not using contraception. Safety and efficacy in pregnant women has not been established.

The following symptoms may occur in the newborn after maternal use of BRINTELLIX 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 BRINTELLIX treatment, this

potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Breastfeeding

Mothers should not breastfeed their infants when taking BRINTELLIX. The safety of BRINTELLIX 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 BRINTELLIX 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 BRINTELLIX (5 to 20 mg/day), and for which the incidence in patients treated with BRINTELLIX 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**				
	BRINTELLIX **5 mg/day (n=1157)**	BRINTELLIX **10 mg/day (n=1042)**	BRINTELLIX **15 mg/day (n=449)**	BRINTELLIX **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 BRINTELLIX 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

BRINTELLIX 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 BRINTELLIX.

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 BRINTELLIX.

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 BRINTELLIX on a single occasion.

The clinical studies included subjects who were administered 40 to 75 mg. Ingestion of BRINTELLIX 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 BRINTELLIX overdoses of up to 80 mg. The most frequently reported symptoms were nausea and vomiting.

There is limited experience with BRINTELLIX 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).

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).

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 based on renal function (see Section 4.2 and 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 C_{max} 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 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

BRINTELLIX 5 mg, 10 mg, 15 mg and 20 mg 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: 48/1.2/0429

10 mg: 48/1.2/0430

15 mg: 48/1.2/0431

20 mg: 48/1.2/0432

9. DATE OF FIRST AUTHORISATION

3 October 2014

10. DATE OF REVISION OF THE TEXT

22 November 2022

Namibia and Botswana, only:

Botswana: S2: BOT 1502705 (10 mg); BOT 1502706 (20 mg)
Namibia: NS 3: 15/1.2/0071 (10 mg); 15/1.2/0072 (20 mg)