1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VORTIOXETINE 5 mg ASPEN film-coated tablets

VORTIOXETINE 10 mg ASPEN film-coated tablets

VORTIOXETINE 20 mg ASPEN film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VORTIOXETINE 5 mg ASPEN:

Each film-coated tablet contains 6,355 mg vortioxetine hydrobromide equivalent to 5 mg of vortioxetine.

Contains sugar: Mannitol: 11,250 mg per tablet

VORTIOXETINE 10 mg ASPEN:

Each film-coated tablet contains 12,710 mg vortioxetine hydrobromide equivalent to 10 mg of vortioxetine.

Contains sugar: Mannitol: 22,500 mg per tablet

VORTIOXETINE 20 mg ASPEN:

Each film-coated tablet contains 25,42 mg vortioxetine hydrobromide equivalent to 20 mg of vortioxetine.

Contains sugar: Mannitol: 45,00 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

VORTIOXETINE 5 mg ASPEN:

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

VORTIOXETINE 10 mg ASPEN:

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

VORTIOXETINE 20 mg ASPEN:

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology

Adults

VORTIOXETINE ASPEN is for use in adults.

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

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

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

Special populations

Elderly population

The safety and efficacy of VORTIOXETINE ASPEN 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.

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).

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. VORTIOXETINE ASPEN has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients (see section 5.2).

Cytochrome P450 inhibitors

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

Cytochrome P450 inducers

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

Paediatric population

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

Method of administration

For oral administration.

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

4.3. Contraindications

VORTIOXETINE ASPEN is contraindicated in:

- Patients with hypersensitivity to vortioxetine or to any excipients in VORTIOXETINE ASPEN (see section 6.1).
- Concomitant use of VORTIOXETINE ASPEN with monoamine oxidase inhibitors (MAOIs) (see section 4.5).

4.4. Special warnings and precautions for use

Use in paediatric population

VORTIOXETINE ASPEN is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of VORTIOXETINE ASPEN 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 and 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 ASPEN, 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 ASPEN. 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 ASPEN 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 ASPEN. Therefore, VORTIOXETINE ASPEN should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment with VORTIOXETINE ASPEN should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.

Serotonin syndrome and neuroleptic malignant syndrome

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS), potentially life-threatening conditions, may occur with VORTIOXETINE ASPEN. 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 sections 4.3 and 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 VORTIOXETINE ASPEN 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 medicines known to cause hyponatraemia.

Discontinuation of VORTIOXETINE ASPEN should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Activation of hypomania or mania

VORTIOXETINE ASPEN 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 withVORTIOXETINE ASPEN. Caution is advised in patients taking anticoagulants and/or medicines 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.

Risk of postpartum haemorrhage

Literature has shown evidence of a risk of postpartum haemorrhage associated with the use of selective serotonin reuptake inhibitors (SSRIs), such as VORTIOXETINE ASPEN, and selective non-serotonin reuptake inhibitors (SNRIs). The observed relative risk demonstrated point estimates signifying an increasing risk when the use of an antidepressant is closer to the date of delivery.

Co-administration with cytochrome P450 inhibitors

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

Renal impairment

Limited data are available for patients with severe renal impairment. Caution should therefore be exercised.

Hepatic impairment

VORTIOXETINE ASPEN has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients.

4.5. Interaction with other medicines and other forms of interaction

Vortioxetine, as contained in VORTIOXETINE ASPEN 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, VORTIOXETINE ASPEN is contraindicated in any combination with MAOIs. VORTIOXETINE ASPEN must not be initiated for at least 14 days after discontinuation of treatment with an MAOI. VORTIOXETINE ASPEN 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 VORTIOXETINE ASPEN. 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 VORTIOXETINE ASPEN can lower the seizure threshold. Caution is advised when concomitantly using VORTIOXETINE ASPEN and other medicines 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 VORTIOXETINE ASPEN and ECT, therefore caution is advisable.

Cytochrome P450 inhibitors

The exposure to vortioxetine increased 2,3-fold for AUC when Vortioxetine 10 mg Aspen/day was co-administered with bupropion (a strong CYP2D6 inhibitor) 150 mg twice daily for 14 days in 44 healthy patients. The co-administration resulted in a higher incidence of adverse reactions when bupropion was added to VORTIOXETINE ASPEN than when VORTIOXETINE ASPEN was added to bupropion. Depending on individual patient response, a lower dose of VORTIOXETINE ASPEN may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE ASPEN treatment (see section 4.2).

When VORTIOXETINE 10 mg ASPEN/day was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) in 17 healthy patients, a 1,3-fold increase in vortioxetine AUC was observed. No dose adjustment is needed. When VORTIOXETINE 10 mg ASPEN/day was co-administered following 6 days of fluconazole 200 mg/day (a CYP2C9, CYP2C19 and CYP3A4/5 inhibitor) in 16 healthy patients, 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 ASPEN (10 mg/day) in 15 healthy patients.

Cytochrome P450 inducers

When a single dose of VORTIOXETINE 20 mg ASPEN was co-administered following 10 days of rifampicin 600 mg/day (a broad inducer of CYP isozymes) in 14 healthy patients, 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 toVORTIOXETINE ASPEN treatment (see section 4.2).

Aspirin

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

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 10 mg ASPEN/day for 14 days with stable doses of warfarin in 52 healthy patients. 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 10 mg ASPEN/day administration in 28 healthy patients. However, caution should be exercised when VORTIOXETINE ASPEN 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).

Alcohol

No significant additional impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for VORTIOXETINE ASPEN single doses of 20 and 40 mg following co-administration with a single dose of ethanol 0,6 g/kg in 55 healthy patients. 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 ASPEN following co-administration of Vortioxetine 10 mg Aspen/day with a single 10 mg dose of diazepam in 32 healthy patients.

Oral contraceptives

No significant effects, relative to placebo, were observed in the levels of sex hormones following co-administration of VORTIOXETINE 10 mg ASPEN/day with a combined oral contraceptive (ethinyl oestradiol 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 Pharmacokinetic properties). No inhibitory effect of VORTIOXETINE ASPEN (10 mg/day for 14 days) was observed in healthy patients for the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP2C9 (warfarin), CYP3A4/5 (ethinyl oestradiol), or CYP2B6 (bupropion). In a medicine interaction study in healthy patients, no inhibitory effect of VORTIOXETINE 10 mg

ASPEN/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 coadministration with VORTIOXETINE 10 mg ASPEN/day for 14 days in 16 healthy patients. However, there have been reports of enhanced effects when antidepressants with serotonergic effect such as VORTIOXETINE ASPEN have been given together with lithium or tryptophan, therefore concomitant use of VORTIOXETINE ASPEN with these medicines should be undertaken with caution.

4.6. Fertility, pregnancy and lactation

Pregnancy

VORTIOXETINE ASPEN's safety and efficacy in pregnant women has not been established. The following symptoms may occur in the newborn after maternal use of VORTIOXETINE ASPEN 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 ASPEN 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 ASPEN 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.

Human case reports with other medicines from related pharmacological class of antidepressants (SSRIs) have been shown.

4.7. Effects on ability to drive and use machines

VORTIOXETINE ASPEN has no or negligible influence on the ability to drive and use machines. However, 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 or when changing the dose.

4.8. Undesirable effects

a) Summary of the safety profile

The most common adverse reaction was nausea. Adverse reactions were 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.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent
Metabolism and nutrition disorders	Decreased appetite	
Psychiatric disorders	Abnormal dreams	Bruxism
Nervous system disorders	Dizziness	
Vascular disorders		Flushing
Gastrointestinal disorders	Nausea, diarrhoea, constipation, vomiting	
General disorders and administrative site conditions	Generalised pruritus	Night sweats

c) Post-marketing adverse reactions

System organ class	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations	Anaphylactic reaction
Immune system disorders	Angioedema
Metabolism and nutrition disorders	Hyponatraemia
Nervous system disorders	Serotonin Syndrome
Vascular disorders	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding),
	risk of postpartum haemorrhage
Skin and subcutaneous tissue disorders	Urticaria, rash

d) Description of selected adverse reactions

Sexual dysfunction

VORTIOXETINE ASPEN 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 ASPEN.

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 ASPEN.

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/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

There is limited experience with VORTIOXETINE ASPEN overdose.

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

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

Treatment

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)

Pharmacotherapeutic group: Other antidepressants, Vortioxetine

ATC code: N06AX26

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 AUC0-24h 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 populations

Elderly

In elderly healthy patients (aged ≥ 65 years; n=20), the exposure to vortioxetine increased up to 27 % (Cmax and AUC) compared to young healthy control patients (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 (see section 4.2).

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).

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

VORTIOXETINE 5 mg, 10 mg and 20 mg ASPEN tablets contain

colloidal silicone dioxide, hydroxypropyl cellulose, hypromellose, macrogol, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate, titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

10 tablets are sealed with PVC/PVdC base foil on one side and aluminium lid foil on the other side in the form of Alu-PVC/PVdC blisters and such 1 or 3 blister packs are further packed in a printed carton along with instructions for use. Pack-sizes of 10 or 30 film-coated tablets.

14 tablets are sealed with PVC/PVdC base foil on one side and aluminium lid foil on the other side in the form of Alu-PVC/PVdC blisters and such 1 or 2 blister packs are further packed in a printed carton along with instructions for use. Pack-sizes of 14 or 28 film-coated tablets.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

VORTIOXETINE 5 mg ASPEN: 54/1.2/0702

VORTIOXETINE 10 mg ASPEN: 54/1.2/0703

VORTIOXETINE 20 mg ASPEN: 54/1.2/0704

9. DATE OF FIRST AUTHORISATION

22 November 2022

10. DATE OF REVISION OF TEXT

22 November 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088

ZA_VORTTAB_2211_00