Professional Information for VORTIOXETINE ZYDUS

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VORTIOXETINE 5 ZYDUS film-coated tablets

VORTIOXETINE 10 ZYDUS film-coated tablets

VORTIOXETINE 20 ZYDUS film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains 5,6 mg mannitol (sugar alcohol) per film-coated tablet.

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

Contains 5,8 mg mannitol (sugar alcohol) per film-coated tablet.

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

Contains 11,7 mg mannitol (sugar alcohol) per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VORTIOXETINE 5 ZYDUS: Peach to pink coloured, oval, film-coated tablet, debossed with “13” on one side and “19” on the other side.

VORTIOXETINE 10 ZYDUS: Yellow coloured, oval, film-coated tablet, debossed with “1320” on one side and plain on the other side.

VORTIOXETINE 20 ZYDUS: Orange coloured, oval film-coated tablet, debossed with “1322” on one

side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adults

VORTIOXETINE ZYDUS is for oral use in adults.

The initial 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 VORTIOXETINE ZYDUS without the need for a gradual reduction in dose.

Elderly patients

The safety and efficacy of VORTIOXETINE ZYDUS have been established in elderly patients. Caution is however advised when treating these patients. Treatment should be initiated with the minimum dose of 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 eldery are limited (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required in patients with renal impairment or end-stage renal disease. However, when treating patients with severe renal insufficiency, caution is advised (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. VORTIOXETINE ZYDUS have not been studied in patients with severe hepatic impairment and caution is therefore advised when VORTIOXETINE ZYDUS is prescribed to these patients (see section 5.2).

Cytochrome P450 (CYP450) inhibitors

If strong CYP2D6 inhibitors (such as bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE ZYDUS treatment, a lower dose of VORTIOXETINE ZYDUS may be considered depending on individual patient response (see section 4.5).

Cytochrome P450 inducers

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

Paediatric patients

The safety and efficacy of VORTIOXETINE ZYDUS in children and adolescents under 18 years of age have not been established (see section 4.4).

Method of administration

VORTIOXETINE ZYDUS should be taken orally once a day, with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 resmission occurs. Improvement may not be present during the initial few weeks or more of treatment with VORTIOXETINE ZYDUS 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.

Close supervision of patients and in particular those at high risk should accompany treatment 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

There is a potential risk of seizures with the use of antidepressants including VORTIOXETINE ZYDUS. In patients with a history of seizures or unstable epilepsy, VORTIOXETINE ZYDUS 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 the use of VORTIOXETINE ZYDUS. An increased risk for SS or NMS results from the concurrent use of VORTIOXETINE ZYDUS 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 VORTIOXETINE ZYDUS should be discontinued immediately and symptomatic treatment should be started.

Mania/hypomania

Caution is advised with VORTIOXETINE ZYDUS 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 ZYDUS, 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.

Haemmorhage

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and other haemmorrhagic events, such as gastrointestinal or gynaecological bleeding with the use of antidepressants with serotonergic effect, including VORTIOXETINE ZYDUS. Caution is advised with VORTIOXETINE ZYDUS 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 acetylsalicylic

acid (ASA)) (see section 4.5). Caution is also advised in patients with known bleeding disorders or tendencies.

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.
In patients presenting with symptomatic hyponatraemia, the discontinuation of treatment with VORTIOXETINE ZYDUS should be considered and medical intervention introduced.

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 VORTIOXETINE ZYDUS 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 VORTIOXETINE ZYDUS in elderly patients with major depressive episodes are limited (see sections 4.2, 4.8 and 5.2).

Renal or hepatic impairment

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

Paediatric population

The safety and efficacy of vortioxetine, as in VORTIOXETINE ZYDUS, have not been established in

patients under 18 years of age and the treatment of depression with VORTIOXETINE ZYDUS 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.

4.5 Interaction with other medicines and other forms of interaction

VORTIOXETINE ZYDUS undergoes extensive hepatic metabolism, primarily through oxidation (catalysed by CYP2D6 and to a minor extent, CYP3A4/5 and CYP2C9) and subsequent glucuronic acid conjugation (see section 5.2).

MAOIs

The concomitant use of VORTIOXETINE ZYDUS with MAOIs should be avoided due to the risk of serotonin syndrome. Following the discontiuation of treatment with an MAOI, a waiting period of at least 14 days is required before treatment with VORTIOXETINE ZYDUS can be initiated. VORTIOXETINE ZYDUS must be discontinued for at least 14 days before treatment with an MAOI can be initiated.

Linezolid

The combination of vortioxetine with a MAOI, such as the antibiotic linezolid, is contraindicated (see section 4.3). If the combination proves essential, the added medicine should be given with minimum dosage and under close clinical monitoring for serotonin syndrome (see section 4.4).

Serotonergic medicines

Serotonin syndrome may result from the co-administration of VORTIOXETINE ZYDUS and medicines with serotonergic effect, such as pethidine, tramadol, sumatriptan and other triptans (see section 4.4).

St John's wort

A higher incidence of adverse reactions, including serotonin syndrome (SS), may result from the concomitant use of antidepressants with serotonergic effect and herbal remedies containing St John's wort (*Hypericum perforatum*).

Medicines lowering the seizure threshold

The threshold for seizures can be lowered by antidepressants with serotonergic effect including VORTIOXETINE ZYDUS. Caution is therefore advised in the co-administration of VORTIOXETINE ZYDUS 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 VORTIOXETINE ZYDUS and ECT.

CYP2D6 inhibitors

The exposure to vortioxetine increased 2,3-fold for area under the curve (AUC) when vortioxetine 10 mg per day was co-administered with bupropion (a strong CYP2D6 inhibitor 150 mg twice daily) for 14 days in healthy subjects. Co-administration resulted in a higher incidence of adverse reactions when bupropion was added to vortioxetine than when vortioxetine was added to bupropion. Depending on individual patient response, a lower dose of VORTIOXETINE ZYDUS may be considered if strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to VORTIOXETINE ZYDUS treatment (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 1,5-fold increase, respectively, in vortioxetine AUC

was observed. No dose adjustment is required when co-administering VORTIOXETINE ZYDUS with a CYP3A4/5, CYP2C9 or CYP2C19 inhibitor.

Studies show that a 40 mg single-dose omeprazole (CYP2C19 inhibitor) in healthy subjects had no inhibitory effect on the multiple-dose pharmacokinetics of vortioxetine.

Interactions with strong CYP3A4 inhibitors and CYP2C9 ihibitors in CYP2D6 poor metabolisers

It is anticipated that the concomitant use of VORTIOXETINE ZYDUS and strong inhibitors of CYP3A4 (such as itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, conivaptan and many of the HIV protease inhibitors) or inhibitors of CYP2C9 (such as fluconazole and amiodarone) and poor CYP2D6 metabolisers (see section 5.2) may result in a more marked increased exposure of VORTIOXETINE ZYDUS as compared to the moderate effect described above. The concurrent use of VORTIOXETINE ZYDUS and strong inhibitors of CYP3A4 or inhibitors of CYP2C9 in poor CYP2D6 metabolisers has not been investigated specifically.

Depending on individual patient response, a lower dose of VORTIOXETINE ZYDUS may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in CYP2D6 poor metabolisers.

Cytochrome P450 inducers

During studies, a 72 % decrease in AUC of vortioxetine was observed 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. Depending on individual patient response, a dose adjustment of VORTIOXETINE ZYDUS may therefore be considered if a broad cytochrome P450 inducer (such as rifampicin, carbamazepine, phenytoin) is added to VORTIOXETINE ZYDUS 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 VORTIOXETINE ZYDUS 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 VORTIOXETINE ZYDUS on other medicine

Anticoagulants and antiplatelet medicines

Studies show that following the co-administration of multiple doses of vortioxetine with stable doses of warfarin in healthy subjects, no significant effects are observed in international normalised ratio (INR), prothrombin or plasma R-/S-warfarin values, relative to placebo. When acetylsalicylic acid 150 mg/day was co-administered following multiple doses of vortioxetine administration in healthy subjects, no significant inhibitory effect on platelet aggregation or pharmacokinetics of acetylsalicylic acid or salicylic acid was observed, in comparison to the placebo. The potential increased risk of bleeding due to pharmacodynamic interaction can however not be neglected and caution is therefore advised when VORTIOXETINE ZYDUS is co-administered with oral anticoagulant or antiplatelet medicines (see section 4.4).

Cytochrome P450 substrates

According to *in vitro* studies, VORTIOXETINE ZYDUS 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.

The co-administration of vortioxetine 10 mg/daily with a single 10 mg dose of diazepam did not result in any pharmacodynamic interactions or significant cognitive function impairment, in comparison to placebo.
When vortioxetine 10 mg/daily was co-administered with a combined oral contraceptive (ethinyl estradiol 30 µg/levonorgestrel 150 µg) and compared to placebo, no considerable effects in the levels of sex hormones could be observed.

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 VORTIOXETINE ZYDUS 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, as in VORTIOXETINE ZYDUS. 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
The use of VORTIOXETINE ZYDUS should be avoided during pregnancy, as the safety and efficacy in pregnant women have not been established. Studies in animals have indicated reproductive toxicity.

The maternal use of a serotoninergic medicine, such as VORTIOXETINE ZYDUS, in the later stages of pregnancy may result in newborn symptoms, such as respiratory distress, cyanosis, apnoea,

seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. In most cases, these complications were found to begin immediately or soon after delivery (less than 24 hours). These symptoms could be due to either the effects resulting from the discontinuation of the serotonergic medicine, or the excess of serotonergic activity.

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 VORTIOXETINE ZYDUS have not been studied and the potential risk should therefore not be neglected, considering the related mechanism of action of VORTIOXETINE ZYDUS (increase in serotonin concentrations).

Breastfeeding

The safety of VORTIOXETINE ZYDUS during breastfeeding has not been established. The excretion of VORTIOXETINE ZYDUS into human milk is however anticipated, as the excretion of vortioxetine and/or vortioxetine metabolites have been demonstrated by available animal data. The risk to the breastfeeding infant can therefore not be neglected.

Fertility

The effect of VORTIOXETINE ZYDUS on human fertility has not been studied.

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 VORTIOXETINE ZYDUS 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*

Metabolism and nutrition disorders

Frequent: decreased appetite

Frequency unknown: hyponatraemia*

Psychiatric disorders

Frequent: abnormal dreams

Less frequent: bruxism

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

Nervous system disorders

Frequent: dizziness

Frequency unknown: serotonin syndrome*

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)

Less frequent: night sweats

Frequency unknown: urticaria*, rash*

*Based on post-marketing experience.

Description of selected adverse reactions

Nausea

Clinical trials with vortioxetine indicate that nausea was experienced early in the treatment (within the first two weeks) and was usually mild or moderate. The nausea generally passed and did not result in discontinuation of the therapy. It was however found that women experienced a higher frequency of gastrointestinal adverse reactions (such as nausea), in comparison to men.

Elderly patients

Clinical studies with ≥ 10 mg vortioxetine once daily showed that patients aged 65 years or more had a higher rate of withdrawal from the studies. Elderly patients (≥ 65 years) also experienced a higher incidence of nausea and constipation when receiving doses of 20 mg vortioxetine once daily, than younger 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

Data from epidemiological studies show an increased risk of bone fractures in patients receiving a medicine from related pharmacological classes of antidepressants (SSRIs or TCAs). These studies were primarily conducted in patients aged 50 years and older. As the mechanism of action for this risk is unknown, in is uncertain whether the treatment with VORTIOXETINE ZYDUS may result in the same risk.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VORTIOXETINE ZYDUS is important. It allows continued monitoring of the benefit/risk balance of VORTIOXETINE ZYDUS. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **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

Experience with VORTIOXETINE ZYDUS overdose is limited.

Clinical studies with vortioxetine indicate that doses of 40 – 75 mg can cause augmentation of adverse effects, such as nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritis, somnolence and flushing.

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

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Nonclinical data indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A 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, dopamine, histamine, acetylcholine, GABA and glutamate systems.

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 (Vss) 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 catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9 and subsequent glucuronic acid conjugation.
No inhibitory or inducing effect of vortioxetine was observed in the interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 (see section 4.5). 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 ⅔ of the inactive vortioxetine metabolites are excreted in the urine and approximately ⅓ in the faeces. Only negligible amounts of vortioxetine are excreted in the faeces. 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_{0-24h} following multiple doses of 5 to 20 mg/day.

Special 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. The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years (see section 4.2). However, caution should be exercised when prescribing to elderly patients at doses higher than 10 mg vortioxetine once daily (see section 4.4).

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, respectively; 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 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

The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. Co-administration of strong CYP3A4/2C9 inhibitors to 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.
Depending on individual patient response, a dose adjustment may be considered (see section 4.2).

5.3. Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Crospovidone

Magnesium stearate

Mannitol

Microcrystalline cellulose

Silicon dioxide.

VORTIOXETINE 5 ZYDUS:

Tablet coating (Opadry Pink):

Hypromellose (E464)

Iron oxide red (E172)

Iron oxide yellow (E172)

Macrogol (E1521)

Titanium dioxide (E171).

VORTIOXETINE 10 ZYDUS:

Tablet coating (Opadry Yellow):

D&C Yellow Nr. 10 Aluminium Lake

Hypromellose (E464)

Iron oxide yellow (E172)

Macrogol (E1521)

Titanium dioxide (E171).

VORTIOXETINE 20 ZYDUS:

Tablet coating (Opadry Orange):

D&C Yellow Nr. 10 Aluminium Lake

FD&C Red Nr. 40/Allura Red AC Aluminium Lake

Hypromellose (E464)

Iron oxide red (E172)

Macrogol (E1521)

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep bottle tightly closed until required for use.

6.5 Nature and contents of container

White, high-density polyethylene (HDPE), round bottle, closed with a white child resistant polypropylene (PP) cap, having ribs on the sides, and opening / closing instructions embossed on top and a continuous threaded inner cap.

Pack size	HDPE bottle	PP cap
VORTIOXETINE 5 ZYDUS		
30 tablets	60 mL	33 mm
90 tablets	60 mL	33 mm
500 tablets	75 mL	38 mm
VORTIOXETINE 10 ZYDUS		
30 tablets	60 mL	33 mm
90 tablets	60 mL	33 mm
500 tablets	100 mL	38 mm
VORTIOXETINE 20 ZYDUS		
30 tablets	60 mL	33 mm
90 tablets	60 mL	33 mm
500 tablets	200 mL	38 mm

6.6 Special precautions for disposal and other handling

VORTIOXETINE ZYDUS does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare S.A. (Pty) Ltd

Southdowns Office Park,

Building B, Ground Floor

22 Karee Street

Centurion

0157

8. REGISTRATION NUMBERS

VORTIOXETINE 5 ZYDUS: 55/1.2/0794.791

VORTIOXETINE 10 ZYDUS: 55/1.2/0795.972

VORTIOXETINE 20 ZYDUS: 55/1.2/0796/793

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023.

10. DATE OF REVISION OF THE TEXT