Clean Professional Information

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VORTIOXETINE 5 ADCO 5 mg Film-coated tablets

VORTIOXETINE 10 ADCO 10 mg Film-coated tablets

VORTIOXETINE 20 ADCO 20 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VORTIOXETINE 5 ADCO:

Each film-coated tablet contains vortioxetine hydrobromide equivalent to 5 mg vortioxetine.

VORTIOXETINE 10 ADCO:

Each film-coated tablet contains vortioxetine hydrobromide equivalent to 10 mg vortioxetine.

VORTIOXETINE 20 ADCO:

Each film-coated tablet contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

- VORTIOXETINE 5 ADCO: Contains sugar (mannitol): 12,5 mg per film-coated tablet.
- VORTIOXETINE 10 ADCO: Contains sugar (mannitol): 25,0 mg per film-coated tablet.
- VORTIOXETINE 20 ADCO: Contains sugar (mannitol): 50 mg per film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VORTIOXETINE 5 ADCO:

Pink, almond-shaped, biconvex film-coated tablet debossed with "L" on one side and “07” on the other side (approximately 6,0 mm in length and 3,3 mm in width).

VORTIOXETINE 10 ADCO:

Yellow, almond-shaped, biconvex film-coated tablet debossed with "L" on one side and “08” on the other side (approximately 7,2 mm in length and 4,2 mm in width).

VORTIOXETINE 20 ADCO:

Red, almond-shaped, biconvex film-coated tablet debossed with ‘612’ on one side and plain on other side (approximately 8,8 mm in length and 5,2 mm in width).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The starting and recommended dose of VORTIOXETINE ADCO is 10 mg once daily. Depending on the 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 treatment. A dose decrease may be considered for patients who do not tolerate higher doses.

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

Treatment discontinuation

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

Special populations

Elderly patients

The safety and efficacy of VORTIOXETINE ADCO 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 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 ADCO has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients (see section 5.2).

Paediatric population

The safety and efficacy of VORTIOXETINE ADCO in children and adolescents aged less than 18 years have not been established.

No data are available.

Cytochrome P450 inhibitors

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

Cytochrome P450 inducers

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

Method of administration

VORTIOXETINE ADCO is for oral use in adults.

VORTIOXETINE ADCO can be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to vortioxetine or to any of the excipients listed in section 6.1.

Concomitant use with nonselective monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population

VORTIOXETINE ADCO is not recommended in patients aged less than 18 years for the treatment of depression since the safety and efficacy of vortioxetine have not been established in this age group (see section 4.2).

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 continues until significant remission occurs. Patients should be closely monitored until improvement occurs, as improvement may not occur during the first few weeks or more of treatment with vortioxetine. 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. A meta-analysis of placebo-controlled clinical studies 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 of age.

Close supervision of patients and in particular those at high risk should accompany treatment with VORTIOXETINE ADCO 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 ADCO. Therefore, VORTIOXETINE ADCO should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy (see section 4.5). Treatment should be discontinued in any patient who develops seizures or for whom there is an increase in seizure frequency.

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS), potentially life-threatening conditions, may occur with VORTIOXETINE ADCO. The risk of SS or NMS is increased with concomitant use of serotonergic-active substances (including triptans), medicines that impair the 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 include autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea), mental status changes (e.g., agitation, hallucinations, coma) and/or neuromuscular aberrations (e.g., hyperreflexia, incoordination). If this occurs, treatment with VORTIOXETINE ADCO should be discontinued immediately and symptomatic treatment should be initiated.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported less frequently with the use of antidepressants with serotonergic effect (SSRIs, SNRIs). Caution should be exercised in patients at risk, such as the elderly,

patients with cirrhosis of the liver or patients concomitantly treated with medicines known to cause hyponatraemia.

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

Activation of hypomania or mania

VORTIOXETINE ADCO 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, have been reported less frequently with the use of antidepressants with serotonergic effect, including VORTIOXETINE ADCO. 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), aspirin (acetylsalicylic acid – ASA)] (see section 4.5) and in patients with known bleeding tendencies/disorders.

Co-administration with cytochrome P450 inhibitors

Co-administration of VORTIOXETINE ADCO and bupropion resulted in a higher incidence of adverse reactions when bupropion was added to VORTIOXETINE ADCO than when VORTIOXETINE ADCO as added to bupropion (see section 4.5).

Depending on individual patient response, a lower dose of VORTIOXETINE ADCO may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to VORTIOXETINE ADCO treatment (see sections 4.2 and 4.5).

Elderly

Data on the use of vortioxetine (as in VORTIOXETINE ADCO) in elderly patients with major depressive episodes are limited. Therefore, caution should be exercised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily (see sections 4.2, 4.8 and 5.2).

Renal impairment

Limited data are available for patients with severe renal impairment. Caution should therefore be exercised (see section 5.2).

Hepatic impairment

Vortioxetine (as in VORTIOXETINE ADCO) has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients (see section 5.2).

4.5 Interactions 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).

Potential for other medicines to affect vortioxetine

Irreversible non-selective MAOIs

Due to the risk of serotonin syndrome, VORTIOXETINE ADCO is contraindicated in any combination with irreversible non-selective MAOIs (see section 4.3). VORTIOXETINE ADCO must not be initiated for at least 14 days after discontinuation of treatment with an irreversible nonselective
MAOI. VORTIOXETINE ADCO must be discontinued for at least 14 days before starting treatment with an irreversible non-selective MAOI (see section 4.3).

Reversible, selective MAO-A inhibitor (moclobemide)

The combination of VORTIOXETINE ADCO with a reversible and selective MAO-A inhibitor, such as moclobemide, is contraindicated (see section 4.3). If the combination proves necessary, the added medicine should be given with minimum dosage and under close clinical monitoring for serotonin syndrome (see section 4.4).

Reversible, non-selective MAOI (linezolid)

The combination of VORTIOXETINE ADCO with a weak reversible and non-selective MAOI, such as the antibiotic linezolid, is contraindicated (see section 4.3). If the combination proves necessary, the added medicine should be given with minimum dosage and under close clinical monitoring for serotonin syndrome (see section 4.4).

Irreversible, selective MAO-B inhibitor (selegiline, rasagiline)

Although a lower risk of serotonin syndrome is expected with selective MAO-B inhibitors than with MAO-A inhibitors, the combination of VORTIOXETINE ADCO with irreversible MAO-B inhibitors, such as selegiline or rasagiline should be administered

with caution. 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 ADCO, can lower the seizure threshold. Caution is advised when concomitantly using VORTIOXETINE ADCO and other medicines capable of lowering the seizure threshold [e.g., antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion, tramadol] (see section 4.4).

ECT (electroconvulsive therapy)

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

CYP2D6 inhibitors

The exposure to vortioxetine increased 2,3-fold for area under the curve (AUC) when vortioxetine (as in VORTIOXETINE ADCO) 10 mg/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 (as in VORTIOXETINE ADCO) than when vortioxetine (as in VORTIOXETINE ADCO) was added to bupropion. Depending on individual patient response, a lower dose of VORTIOXETINE ADCO may be considered if a strong CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is added to VORTIOXETINE ADCO treatment (see section 4.2).

CYP3A4 inhibitors and CYP2C9, and CYP2C19 inhibitors

When vortioxetine (as in VORTIOXETINE ADCO) 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 CYP2C9, CYP2C19, and CYP3A4/5 inhibitor) in healthy subjects, a 1,3-fold and 1,5-fold increase, respectively, in vortioxetine 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 (as in VORTIOXETINE ADCO) in healthy subjects.

Interactions in CYP2D6 poor metabolisers

Co-administration of strong inhibitors of CYP3A4 (such as itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, conivaptan and many of the HIV protease inhibitors) and inhibitors of CYP2C9 (such as fluconazole and amiodarone) to CYP2D6 poor metabolisers (see section 5.2) has not been investigated specifically, but it is anticipated that it will lead to a more marked increased exposure of vortioxetine (as in

VORTIOXETINE ADCO) in these patients as compared to the moderate effect described above. Depending on individual patient response, a lower dose of VORTIOXETINE ADCO may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in CYP2D6 poor metabolisers.

Cytochrome P450 inducers

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

Alcohol

No effect on the pharmacokinetics of vortioxetine or ethanol and no significant impairment, relative to placebo, in cognitive function were observed when vortioxetine (as in VORTIOXETINE ADCO) in a single dose of 20 mg or 40 mg was co-administered with a single dose of ethanol (0,6 g/kg) in healthy subjects. However, alcohol intake is not advisable during antidepressant treatment.

Acetylsalicylic acid (Aspirin)

No effect of multiple doses of acetylsalicylic acid 150 mg/day on the multiple-dose pharmacokinetics of vortioxetine (as in VORTIOXETINE ADCO) was observed in healthy subjects.

Potential for vortioxetine to affect other medicines

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 multiple doses of vortioxetine with stable doses of warfarin in healthy subjects. Also, no significant inhibitory effect, relative to placebo, on platelet aggregation or pharmacokinetics of acetylsalicylic acid or salicylic acid was observed when acetylsalicylic acid 150 mg/day was co-administered following multiple doses of vortioxetine (as in VORTIOXETINE ADCO) administration in healthy subjects. However, caution should be exercised when VORTIOXETINE ADCO is combined with oral anticoagulants or antiplatelet medicines due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see section 4.4).

Cytochrome P450 substrates

In vitro, vortioxetine (as in VORTIOXETINE ADCO) did not show any relevant potential for inhibition or induction of cytochrome P450 isozymes (see section 5.2).

Following multiple doses of vortioxetine, no inhibitory effect was observed in healthy subjects for the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinyl estradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or CYP2D6 (dextromethorphan).

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

Lithium, tryptophan

No clinically relevant effect was observed during steady-state lithium exposure following co-administration with multiple doses of vortioxetine in healthy subjects. However, there have been reports of enhanced effects when antidepressants with serotonergic effect have been given together with lithium or tryptophan; therefore, concomitant use of VORTIOXETINE ADCO with these medicines should be undertaken with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of vortioxetine in pregnant women.

The safety and efficacy of VORTIOXETINE ADCO in pregnant women has not been established.

Newborn

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

Epidemiological data suggest 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 with VORTIOXETINE ADCO treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Breastfeeding

Available data in animals have shown excretion of vortioxetine/ vortioxetine metabolites into milk. It is expected that vortioxetine will be excreted into human milk.

The safety of VORTIOXETINE ADCO in breastfeeding women has not been established.

Fertility

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

Human case reports with medicines from the related pharmacological class of antidepressants (SSRIs) have shown an effect on sperm quality that is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

VORTIOXETINE ADCO has no or negligible influence on the ability to drive and use machines.

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

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse reaction was nausea.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Immune system disorders	Frequency not known*	Anaphylactic reaction.
Metabolism and nutrition disorders	Frequency not known*	Decreased appetite, hyponatraemia.
Psychiatric disorders	Frequent	Abnormal dreams.
	Less frequent	Bruxism.
Nervous system disorders	Frequent	Dizziness.
	Frequency not known*	Serotonin syndrome.
Vascular disorders	Less frequent	Flushing.
	Frequency not known*	Ecchymosis, epistaxis, haemorrhage (including contusion, gastrointestinal or vaginal bleeding).
Gastrointestinal disorders	Frequent	Constipation, diarrhoea, nausea, vomiting.
Skin and subcutaneous tissue disorders	Frequent	Pruritus, including pruritus generalised.
	Less frequent	Night sweats.
	Frequency not known*	Angioedema, rash, urticaria.

* Based on post-marketing cases

c. Description of selected adverse reactions

Nausea

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

Elderly patients

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

For doses of 20 mg vortioxetine (as in VORTIOXETINE ADCO) once daily, the incidences of nausea and constipation were higher in patients aged ≥ 65 years (42 % and 15 %, respectively) than in patients aged < 65 years (27 % and 4 %, respectively) (see section 4.4).

Sexual dysfunction

Sexual dysfunction (i.e. difficulties with satisfaction of orgasm and ease of sexual arousal) was assessed using the Arizona Sexual Experience Scale (ASEX). Doses of 5 to 15 mg showed no difference to placebo. However, the 20 mg dose of vortioxetine (as in VORTIOXETINE ADCO) was associated with an increase in sexual dysfunction (treatment-emergent sexual dysfunction (TESD)) (see section 5.1).

Class effect

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

ADCO.

d. Paediatric population

No information.

e. Other special population(s)

No information.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is limited experience with VORTIOXETINE ADCO overdosage.
In clinical studies, no patient ingested more than 75 mg vortioxetine (as in VORTIOXETINE ADCO) on a single occasion.

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

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

Paediatric population

No information.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group and ATC code: 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.

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, leading to modulation of neurotransmission in several systems, including predominantly the serotonin but probably also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems.

However, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear.

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, CYP2C9, CYP2C19, CYP2A6, CYP2B6 and CYP2C8 are involved in the metabolism of vortioxetine.

No inhibitory or inducing effect of vortioxetine was observed *in vitro* in the drug-drug 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 2/3 of the 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. 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.

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. 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 4.2 and 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 (see section 4.2 and 4.4).

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 (see section 4.2). Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients (see section 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Hydroxypropyl cellulose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Sodium stearyl fumarate

Coating

VORTIOXETINE 5 ADCO:

Opadry Pink 03F84770, consisting of:

HPMC 2910/Hypromellose

Iron oxide red

Macrogol/PEG

Talc

Titanium dioxide

VORTIOXETINE 10 ADCO:

Opadry Yellow 03F520217, consisting of:

Ferrosoferric oxide / black iron oxide

HPMC 2910/Hypromellose

Iron oxide yellow

Macrogol/PEG

Titanium dioxide

VORTIOXETINE 20 ADCO:

Opadry Brown 03F565072, consisting of:

Ferrosoferric oxide / black iron oxide

HPMC 2910/Hypromellose

Iron oxide red

Macrogol/PEG

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

Do not remove the blister from the carton until required for use.

6.4 Special precautions for storage

VORTIOXETINE ADCO does not require any special storage condition (please refer to section 6.3).

6.5 Nature and contents of container

VORTIOXETINE ADCO is packed in Alu/Alu blister pack of cold form blister (made of OPA film, soft tempered aluminium foil and PVC film) and aluminium foil. Such blisters are further packed in a carton along with the professional information and patient information leaflet.

Available in pack sizes of 28’s and 30’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 / ADCOCK (232625)

8. REGISTRATION NUMBER(S)

VORTIOXETINE 5 ADCO: 55/1.2/0132.129

VORTIOXETINE 10 ADCO: 55/1.2/0133.130

VORTIOXETINE 20 ADCO: 55/1.2/0134.131

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 July 2022

10. DATE OF REVISION OF THE TEXT