APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BRIVOR 5 mg film coated tablet

BRIVOR 10 mg film coated tablet

BRIVOR 20 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BRIVOR 5 mg contains vortioxetine hydrobromide equivalent to 5 mg vortioxetine.

Each 5 mg BRIVOR tablet contains sugar (mannitol 11,250 mg/tablet).

BRIVOR 10 mg contains vortioxetine hydrobromide equivalent to 10 mg vortioxetine.

Each 10 mg BRIVOR tablet contains sugar (mannitol 22,500 mg/tablet).

BRIVOR 20 mg contains vortioxetine hydrobromide equivalent to 20 mg vortioxetine.

Each 20 mg BRIVOR tablet contains sugar (mannitol 45,000 mg/tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

BRIVOR 5 mg are white coloured, round shaped, biconvex, film-coated tablets debossed with "V" on one side and "5" on other side.

BRIVOR 10 mg are white coloured, almond shaped, biconvex, film-coated tablets debossed with "V" on one side and "10" on other side.

BRIVOR 20 mg are white coloured, almond shaped, biconvex, film-coated tablets debossed with "V" on one side and "20" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRIVOR 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 BRIVOR 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 anti-depressive response.

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

Special populations

Elderly patients

The safety and efficacy of BRIVOR 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. BRIVOR 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 BRIVOR may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to BRIVOR treatment (see section 4.5).

Cytochrome P450 inducers

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

Paediatric population

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

No data are available.

Method of administration

The film-coated tablets are for oral use and can be taken with or without food.

Missed dose:

Doctors should advise patients who forget to take BRIVOR to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- hypersensitivity to vortioxetine or to any of the ingredients of BRIVOR listed in section 6.1
- concomitant use with monoamine oxidase inhibitors (MAOIs) selective MAO-A inhibitors (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). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment with BRIVOR, 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 BRIVOR. 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 BRIVOR 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 BRIVOR. Therefore, BRIVOR should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment with BRIVOR 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 BRIVOR. 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 4.4).

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

Activation of hypomania or mania

BRIVOR 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 BRIVOR. 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 vortioxetine and bupropion 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 BRIVOR may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to BRIVOR treatment (see sections 4.2 and 4.5).

Elderly

Data on the use of BRIVOR 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 BRIVOR once daily (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 BRIVOR in these sub-populations are limited, caution should be exercised when treating these patients (see section 4.2 and 5.2).

BRIVOR contains mannitol which may cause a mild laxative effect

Paediatric population

BRIVOR is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of BRIVOR have not been established in this age group. 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.

4.5 Interaction with other medicines and other forms of interaction

Vortioxetine, as contained in BRIVOR, 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).

Contraindicated combinations:

Monoamine Oxidase Inhibitors (MAOIs)

Due to the risk of serotonin syndrome, BRIVOR is contraindicated in any combination

with MAOIs. BRIVOR must not be initiated for at least 14 days after discontinuation of treatment with an MAOI. BRIVOR must be discontinued for at least 14 days before starting treatment with an MAOI (see section 4.3).

***Reversible, selective MAO-A inhibitor (moclobemide)*:**

The combination of BRIVOR 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).

Linezolid (MAOIs):

The antibiotic linezolid is a weak MAOI and should not be given to patients treated with BRIVOR (see section 4.3). Close monitoring for serotonin syndrome is necessary if used concomitantly (see section 4.4).

Potential for other medicines to affect BRIVOR:

Serotonergic medicines

Co-administration of antidepressants and other medicines with 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).

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 BRIVOR 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).

Medicines lowering the seizure threshold

Antidepressants with serotonergic effect including BRIVOR can lower the seizure threshold. Caution is advised when concomitantly using BRIVOR and other medicines capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol (see section 4.4).

ECT (electroconvulsive therapy)

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

Cytochrome P450 inhibitors

CYP2D6 inhibitor

The exposure to vortioxetine increased 2,3-fold for AUC when BRIVOR 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 BRIVOR than when BRIVOR was added to bupropion.

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

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 has not been investigated specifically, but it is anticipated that it will lead to a more marked increased exposure of vortioxetine as in BRIVOR in these patients as compared to the moderate effect described above. Depending on individual patient response, a lower dose of vortioxetine may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in CYP2D6 poor metabolisers.

CYP3A4 inhibitors and CYP2C9, and CYP2C19 inhibitors

When vortioxetine 10 mg/day, as in BRIVOR was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) in 17 healthy subjects or following 6 days of fluconazole 200 mg/day (a CYP2C9, CYP2C19, and CYP3A4/5 inhibitor) in 16 healthy subjects, 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 BRIVOR, in healthy subjects.

Cytochrome P450 inducers

When a single dose of 20 mg BRIVOR 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 BRIVOR treatment (see section 4.2).

Aspirin

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

Alcohol

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

Potential for BRIVOR 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 vortioxetine 10 mg/day, as in BRIVOR 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 following14 days of vortioxetine 10 mg/day, as in BRIVOR, administration in 28 healthy subjects. However, caution should be exercised when BRIVOR 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).

Oral contraceptives

No significant effects, relative to placebo, were observed in the levels of sex hormones following co-administration of vortioxetine 10 mg/day, as in BRIVOR, 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, as in BRIVOR, did not show any relevant potential for inhibition or induction of cytochrome P450 isozymes (see section 5.2).

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

Lithium, tryptophan

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

The following symptoms may occur in the new-born after maternal use of BRIVOR 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 new-born (PPHN).

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

Breastfeeding

The safety of BRIVOR in breastfeeding women has not been established. Available data in animals have shown excretion of vortioxetine/vortioxetine metabolites in milk. It is expected that BRIVOR will be excreted into human milk (see section 5.3).

A risk to the breastfeeding child cannot be excluded.

Fertility

Fertility studies in male and female rats showed no effect of vortioxetine, as in BRIVOR, on fertility, sperm quality or mating performance (see section 5.3).

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:

BRIVOR 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 BRIVOR 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 summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Nasopharyngitis, influenza
Immune system disorders	Frequency unknown	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders	Frequent Frequency unknown	Decreased appetite Hyponatraemia
Psychiatric disorders	Frequent Less frequent	Insomnia, abnormal dreams Bruxism

Nervous system disorders	Frequent Frequency unknown	Headache, dizziness, somnolence, sedation Serotonin syndrome
Vascular disorders	Less frequent Frequency unknown	Flushing Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, dry mouth, constipation, vomiting, dyspepsia, flatulence, abdominal discomfort
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Hyperhidrosis, pruritus generalised Night sweats Urticaria, rash
Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Back pain, arthralgia Bone fractures
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction
General disorders and administrative site conditions	Frequent	Fatigue
Injury, poisoning and procedural complication	Frequent	Accidental overdose

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.

d) Other special populations

Elderly patients

For doses ≥10 mg BRIVOR once daily, the withdrawal rate from the studies was higher in patients aged ≥ 65 years.
For doses of 20 mg BRIVOR once daily, the incidences of nausea and constipation were higher in patients aged ≥ 65 years (than in patients aged < 65 years (see section 4.4).

Sexual Dysfunction

BRIVOR 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. (see section 5.1).

Class effect

Epidemiological studies, mainly conducted inpatients 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 BRIVOR.

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 via the online service for adverse drug reaction reporting by following the link:

https://www.sahpra.org.za/Publications/Index/8

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

There is limited experience with BRIVOR overdose.

In clinical studies, no patient ingested more than 75 mg vortioxetine, as in BRIVOR on a single occasion.

The clinical studies included subjects who were administered 40 to 75 mg and ingestion of BRIVOR in this dose range may cause an aggravation of the following signs and symptoms:

Nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Management of overdose:

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

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants

ATC code: N06AX26

Pharmacological classification: A1.2 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-HT1A 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 micro-dialysis 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 (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 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 ⅔of inactive vortioxetine metabolites are excreted in the urine and approximately ⅓ 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.

Pharmacokinetics in special patient groups

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 (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

Tablet cores:

Colloidal Silicon Dioxide

Hydroxypropyl cellulose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Sodium Starch glycolate

Film coating – Opadry White

HPMC 2910/Hypromellose

Macrogol/PEG

Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

30's pack: 10 tablets of BRIVOR Tablets 5 mg, 10 mg and 20 mg are sealed with PVC/PVdC base foil on one side and Aluminium lid foil on other side in the form of Alu-PVC/PVdC blister and 3 x blister packs are further packed in a printed carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

Brivor 5 mg: A55/1.2/0105

Brivor 10 mg: A55/1.2/0106

Brivor 20 mg: A55/1.2/0107

9. DATE OF FIRST AUTHORISATION

16 May 2023

10. DATE OF REVISION OF THE TEXT