SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

VORZI 20

2. Qualitative and quantitative composition

Vortioxetine Tablets 20 mg: Each film coated tablet contains Vortioxetine Hydrobromide
Equivalent to Vortioxetine…….. 20 mg
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Vortioxetine Tablet 20 mg: 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

Vortioxetine is indicated for the treatment of major depressive episodes in adults.

4.2 Posology and method of administration

Posology

The starting and recommended dose of Vortioxetine is 10 mg Vortioxetine once daily in adults less than 65 years of age.
Depending on individual patient response, the dose may be increased to a maximum of 20 mg Vortioxetine once daily or decreased to a minimum of 5 mg Vortioxetine once daily. After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

Treatment discontinuation

Patients treated with Vortioxetine can abruptly stop taking the medicinal product without the need for a gradual reduction in dose (see section 5.1).

Special populations

Elderly patients

The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily for which data are limited (see section 4.4).

Cytochrome P450 inhibitors

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

Cytochrome P450 inducers

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

Paediatric population

The safety and efficacy of Vortioxetine in children aged 7 to 11 years have not been established. No data are available (see section 4.4). Vortioxetine should not be used in adolescents aged 12 to 17 years with major depressive disorder (MDD) because efficacy has not been demonstrated (see section 5.1). The safety of Vortioxetine in adolescents aged 12 to 17 years is described in section 4.4, 4.8 and 5.1.

Renal or hepatic impairment

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

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance 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

Use in paediatric population

Vortioxetine is not recommended for the treatment of depression in children aged 7 to 11 years since the safety and efficacy of vortioxetine have not been established in this age group. Vortioxetine should not be used in adolescents aged 12 to 17 years with major depressive disorder (MDD) because efficacy has not been demonstrated (see section 5.1). In general, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences reported in adolescents than in adults for abdominal pain-related events and suicidal ideation (see section 4.8 and 5.1). In clinical studies in children and adolescents treated with antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, anger) were more frequently observed than in those treated with placebo.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks

or more of treatment, 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. 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 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

Seizures are a potential risk with antidepressants. Therefore, vortioxetine 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 lifethreatening conditions, may occur with Vortioxetine The risk of SS or NMS is increased with concomitant use of serotonergic-active substances (including triptans), medicinal products 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 sections 4.3 and 4.5).
Serotonin Syndrome symptoms include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, uncoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). If this occurs, treatment with vortioxetine should be discontinued immediately and symptomatic treatment should be initiated.

Mania/hypomania

Vortioxetine should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase.

Aggression/agitation

Patients treated with antidepressants, including vortioxetine, 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.

Haemorrhage

Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events, such as gastrointestinal or gynaecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effect, including Vortioxetine SSRIs/SNRIs may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to vortioxetine (see section 4.6). 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), acetylsalicylic acid (ASA)] (see section 4.5) and in patients with known bleeding tendencies/disorders.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely 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 medicinal products known to cause hyponatraemia.

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

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 to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Elderly

Data on the use of Vortioxetine 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 or hepatic impairment

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

Vortioxetine contains Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9 (see section 5.2).

Potential for other medicinal products to affect vortioxetine

Irreversible non-selective MAOIs

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

Reversible, selective MAO-A inhibitor (moclobemide)

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

Reversible, non-selective MAOI (linezolid)

The combination of vortioxetine 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 medicinal product 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 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 medicinal products

Co-administration of medicinal products with serotonergic effect (e.g., 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). *Medicinal products lowering the seizure threshold*
Antidepressants with serotonergic effect can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products 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 and ECT, therefore caution is advisable.
CYP2D6 inhibitors

The exposure to vortioxetine increased 2.3-fold for area under the curve (AUC) when vortioxetine 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 than when vortioxetine was added to bupropion. Depending on individual patient response, a lower dose of vortioxetine may be considered if strong CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment (see section 4.2).
CYP3A4 inhibitors and 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 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 in healthy subjects.
Interactions in CYP2D6 poor metabolisers

Co-administration of strong inhibitors of CYP3A4 (such as itraconazol, 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 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 coadministered in CYP2D6 poor metabolisers.
Cytochrome P450 inducers

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, 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 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 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

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

Potential for vortioxetine to affect other medicinal products

Anticoagulants and antiplatelet medicinal products

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 administration in healthy subjects. However, caution should be exercised when vortioxetine 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).

Cytochrome P450 substrates

In vitro, vortioxetine 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 coadministration 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 with these medicinal products should be undertaken with caution.
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 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

There are limited data from the use of vortioxetine in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).
The following symptoms may occur in the new born after maternal use of a serotonergic medicinal product 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 treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).
Vortioxetine should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.
Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action (See section 4.4)

Breast-feeding

Available data in animals have shown excretion of vortioxetine/ vortioxetine metabolites in milk. It is expected that vortioxetine will be excreted into human milk (see section 5.3).
A risk to the breastfeeding child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Vortioxetine treatment taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility studies in male and female rats showed no effect of vortioxetine on fertility, sperm quality or mating performance (see section 5.3).
Human case reports with medicinal products 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 has no or negligible influence on the ability to drive and use machines. However, as adverse reactions such as dizziness have been reported, patients should exercise caution when driving or operating hazardous machinery, especially when starting treatment with vortioxetine or when changing the dose.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was nausea.

Tabulated list of adverse reactions

Adverse reactions are listed below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). The list is based on information from clinical trials and post-marketing experience.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Immune system disorders	Not known*	Anaphylactic reaction
Endocrine disorders	Not known*	Hyperprolactinaemia
Metabolism and nutrition disorders	Not known *	Hyponatraemia
Psychiatric disorders	Common	Abnormal dreams
	Not known *	Insomnia
	Not known *	Agitation, aggression (see section 4.4)
Nervous system disorders	Common	Dizziness
	Not known *	Serotonin Syndrome Headache
Eye disorders	Rare	Mydriasis (which may lead to acute narrow angle glaucoma - see section 4.4)
Vascular disorders	Uncommon	Flushing

	Not known*	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus, including pruritus generalised Hyperhidrosis
	Uncommon	Night sweats
	Not known*	Angioedema, Urticaria Rash

* Based on post-marketing cases

Description of selected adverse reactions

Nausea

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

Elderly patients

For doses ≥10 mg vortioxetine once daily, the withdrawal rate from the studies was higher in patients aged ≥65 years.
For doses of 20 mg vortioxetine 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

In clinical studies, sexual dysfunction 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 was associated with an increase in 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 a medicinal product 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

Paediatric population
A total of 308 adolescent patients aged 12 to 17 years with major depressive disorder (MDD) were treated with vortioxetine in a double-blind, placebo-controlled study. In general, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences reported in adolescents than in adults for abdominal pain-related events and suicidal ideation.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose
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.
Post-marketing experience mainly concerns vortioxetine overdoses of up to 80 mg. In the majority of cases, no symptoms or mild symptoms were reported. The most frequently reported symptoms were nausea and vomiting. There is limited experience with vortioxetine overdoses above 80 mg. Following dosages several fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported. Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

5. Pharmacological properties

5.1 Pharmacodynamic properties
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-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, $5HT_{1B}$ 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. This multimodal activity is considered responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed with

vortioxetine in animal studies**.** However, the precise contribution of the individual targets to the observed pharmacodynamics profile remains unclear and caution should be applied when extrapolating animal data directly to man.

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 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 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.

Special populations

Elderly

In elderly healthy subjects (aged ≥65 years; n=20), the exposure to vortioxetine increased up to 27% (Cmax 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 C_{max} were less than 25% lower in all groups. No dose adjustment is needed based on hepatic function (see section 4.2 and 4.4).

CYP2D6 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).

Paediatric population

Pharmacokinetics of vortioxetine in paediatric patients with major depressive disorder following oral administration of 5 to 20 mg once daily was characterized using population modeling analyses based on data from a pharmacokinetic study (7-17 years) and an efficacy and safety study (12-17 years). The pharmacokinetics of vortioxetine in paediatric patients was similar to that observed in adult patients.

5.3 Preclinical safety data
Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose PH 102, Mannitol, Sodium Starch Glycolate Type 'A', Colloidal Silicon Dioxide, Hydroxypropyl Cellulose, Methanol, Dichloromethane , Microcrystalline cellulose PH 112 , Magnesium Stearate and purified water

Tablet coating
Opadry white OY-58900
(HPMC HYPROMELLOSE, TITANIUM DIOXIDE, MACROGOL/PEG)

6.2
Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C. Keep out of reach of children. Protect from moisture

6.5 Nature and contents of container

10 's Alu-PVC/PVdC blister
Pack Size: 1 x 10's ,3 x 10's & 10 x 10's Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER & MANUFACTURING SITE ADDRESS

Manufacturing site:
MSN Laboratories Private Limited,
unit II Sy. No.1277 & 1319 to 1324,
Nandigama(Village),
Kothur (Mandal),

Mahabubnagar District - 509 216.
India

Marketing Authorisation Holder:
SIMBA PHARMACEUTICALS LTD

8. MARKETING AUTHORISATION NUMBER
H2026/CTD12091/24178

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
18/02/2026

10. DATE OF REVISION OF THE TEXT

18/02/2026