Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vortioxetine Krka 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pale greyish pink, oval, biconvex film-coated tablet, marked with 5 on one side.
Tablet dimension: approximately 9 mm x 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vortioxetine Krka 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 Krka 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
A gradual reduction in dosage may be considered to avoid the occurrence of discontinuation symptoms (see section 4.8). However, there is insufficient data to provide specific recommendations for a tapering schedule for patients treated with vortioxetine.

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
Vortioxetine should not be used in paediatric patients (under 18 years of age) with major depressive disorder (MDD) because efficacy has not been demonstrated (see section 5.1). The safety of vortioxetine in paediatric patients 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 Krka 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 should not be used in children and adolescents aged 7 to 17 years with MDD because efficacy has not been demonstrated (see section 5.1). In general, the adverse reaction profile of vortioxetine in children and adolescents was similar to that seen for adults except for a higher incidence of abdominal pain-related events, and a higher incidence of suicidal ideation in adolescents specifically, compared to adults (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 life-threatening conditions, may occur with vortioxetine. The risk of SS or NMS is increased with concomitant use of serotonergic-active substances (including opioids and 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).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, 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 non-selective 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 syndrome (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. opioids (including tramadol) and triptans (including sumatriptan) 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 co-administered 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 or medicines used for pain relief (e.g. acetylsalicylic acid (ASA) or NSAIDs), 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 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 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 newborn 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, in some cases associated with galactorrhoea
Metabolism and nutrition disorders	Not known *	Hyponatraemia
Psychiatric disorders	Common	Abnormal dreams
	Uncommon	Hallucinations
	Not known *	Insomnia
	Not known *	Agitation, aggression (see section 4.4)

Nervous system disorders	Common	Dizziness
	Uncommon	Tremor
	Not known *	Serotonin Syndrome, Headache, Akathisia, Bruxism, Trismus, Restless leg syndrome
Eye disorders	Uncommon	Blurred vision
	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, Dyspepsia
Skin and subcutaneous tissue disorders	Common	Pruritus, including pruritus generalised Hyperhidrosis
	Uncommon	Night sweats
	Not known*	Angioedema, Urticaria, Rash
General disorders and administration site conditions	Not known*	Discontinuation syndrome

* 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). In the post-marketing setting cases of sexual dysfunction have also been reported with doses of vortioxetine below 20 mg.

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 304 children aged 7 to 11 years and 308 adolescents aged 12 to 17 years with major depressive disorder (MDD) were treated with vortioxetine in two double-blind, placebo-controlled studies, respectively. In general, the adverse reaction profile of vortioxetine in children and adolescents was similar to that observed in adults except for a higher incidence of abdominal pain-related events, and a higher incidence of suicidal ideation in adolescents specially, compared to adults (see section 5.1).

Two long-term open-label extension studies were performed with vortioxetine doses of 5 to 20 mg/day, and with a treatment duration of 6 months (N=662) and 18 months (N=94), respectively. Overall, the safety and tolerability profile of vortioxetine in the paediatric population after long-term use was comparable to what has been observed after short-term use.

Symptoms upon discontinuation of vortioxetine treatment
In the clinical studies, discontinuation symptoms were systematically evaluated following abrupt cessation of vortioxetine treatment. There was no clinically relevant difference to placebo in the incidence or nature of the discontinuation symptoms after treatment with vortioxetine (see section 5.1). Cases describing discontinuation symptoms have been reported in the post-marketing setting and have included symptoms such as dizziness, headache, sensory disturbances (including paraesthesia, electric shock sensations), sleep disturbances (including insomnia), nausea and/or vomiting, anxiety, irritability, agitation, fatigue and tremor. These symptoms may occur within the first week of vortioxetine discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
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
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, 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. 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 pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

In humans, two positron emission tomography (PET) studies have been conducted using 5-HT transporter ligands (^{11}C-MADAM or ^{11}C-DASB) to quantify the 5-HT transporter occupancy in the brain across different dose levels. The mean 5-HT transporter occupancy in the raphe nuclei was approximately 50% at 5 mg/day, 65% at 10 mg/day and increased to above 80% at 20 mg/day.

Clinical efficacy and safety

The efficacy and safety of vortioxetine have been studied in a clinical programme that included more than 6,700 patients, of whom more than 3,700 were treated with vortioxetine in short-term

(≤12 weeks) studies of major depressive disorder (MDD). Twelve double-blind, placebo controlled, 6/8-week, fixed-dose studies have been conducted to investigate the short-term efficacy of vortioxetine in MDD in adults (including the elderly). The efficacy of vortioxetine was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D_{24}) total score. This was supported by clinical relevance as demonstrated by the proportions of responders and remitters and the improvement in the Clinical Global Impression – Global Improvement (CGI-I) score. The efficacy of vortioxetine increased with increasing dose.

The effect in the individual studies was supported by the meta-analysis (MMRM) of the mean change from baseline in MADRS total score at Week 6/8 in the short-term, placebo-controlled studies in adults. In the meta-analysis, the overall mean difference to placebo across the studies was statistically significant: -2.3 points (p = 0.007), -3.6 points (p <0.001), and -4.6 points (p <0.001) for the 5, 10, and 20 mg/day doses, respectively; the 15 mg/day dose did not separate from placebo in the meta-analysis, but the mean difference to placebo was -2.6 points. The efficacy of vortioxetine is supported by the pooled responder analysis, in which the proportion of responders ranged from 46% to 49% for vortioxetine versus 34% for placebo (p <0.01; NRI analysis).

Furthermore, vortioxetine, in the dose range of 5-20 mg/day, demonstrated efficacy on the broad range of depressive symptoms (assessed by improvement in all MADRS single–item scores).

The efficacy of vortioxetine 10 or 20 mg/day was further demonstrated in a 12-week, double-blind, flexible-dose comparative study versus agomelatine 25 or 50 mg/day in patients with MDD. Vortioxetine was statistically significantly better than agomelatine as measured by improvement in the MADRS total score and supported by the clinical relevance as demonstrated by the proportions of responders and remitters and improvement in the CGI-I.

Maintenance
The maintenance of antidepressant efficacy was demonstrated in a relapse-prevention study. Patients in remission after an initial 12-week open-label treatment period with vortioxetine were randomised to vortioxetine 5 or 10 mg/day or placebo and observed for relapse during a double-blind period of at least 24 weeks (24 to 64 weeks). Vortioxetine was superior (p=0.004) to placebo on the primary outcome measure, the time to relapse of MDD, with a hazard ratio of 2.0; that is, the risk of relapse was two times higher in the placebo group than in the vortioxetine group.

Elderly
In the 8-week, double-blind, placebo-controlled, fixed-dose study in elderly depressed patients (aged ≥65 years, n=452, 156 of whom were on vortioxetine), vortioxetine 5 mg/day was superior to placebo as measured by improvement in the MADRS and HAM-D_{24} total scores. The effect seen with vortioxetine was a 4.7 point difference to placebo in MADRS total score at Week 8 (MMRM analysis).

Patients with severe depression or with depression and high levels of anxiety symptoms
In severely depressed patients (baseline MADRS total score ≥30) and in depressed patients with a high level of anxiety symptoms (baseline HAM-A total score ≥20) vortioxetine also demonstrated efficacy in the short-term studies in adults (the overall mean difference to placebo in MADRS total score at Week 6/8 ranged from 2.8 to 7.3 points and from 3.6 to 7.3 points, respectively, (MMRM analysis)). In the dedicated study in elderly, vortioxetine was also effective in these patients.
The maintenance of antidepressant efficacy was also demonstrated in this patient population in the long-term relapse prevention study.

Effects of vortioxetine on the Digit Symbol Substitution Test (DSST), the University of California San Diego Performance-Based Skills Assessment (UPSA) (objective measures) and Perceived Deficits Questionnaire (PDQ) and Cognitive and Physical Functioning Questionnaire CPFQ (subjective measures) scores
The efficacy of vortioxetine (5-20 mg/day) in patients with MDD has been investigated in 2 adult and 1 elderly short-term, placebo-controlled studies.

Vortioxetine had a statistically significant effect versus placebo on the Digit Symbol Substitution Test (DSST), ranging from Δ = 1.75 (p = 0.019) to 4.26 (p <0.0001) in the 2 studies in adults and Δ = 2.79 (p = 0.023) in the study in the elderly. In the meta-analyses (ANCOVA, LOCF) of the mean change from baseline in DSST number of correct symbols in all 3 studies, vortioxetine separated from placebo (p<0.05) with a standardised effect size of 0.35. When adjusting for the change in MADRS the total score in the meta-analysis of the same studies showed that vortioxetine separated from placebo (p<0.05) with a standardised effect size of 0.24.

One study assessed the effect of vortioxetine on functional capacity using the University of California San Diego Performance-Based Skills Assessment (UPSA). Vortioxetine separated from placebo statistically with results of 8.0 for vortioxetine versus 5.1 points for placebo (p=0.0003).

In one study, vortioxetine was superior to placebo on subjective measures, evaluated using the Perceived Deficits Questionnaire with results of -14.6 for vortioxetine and -10.5 for placebo (p=0.002). Vortioxetine did not separate from placebo on subjective measures when evaluated using the Cognitive and Physical Functioning Questionnaire with results of -8.1 for vortioxetine versus -6.9 for placebo (p=0.086).

Tolerability and safety
The safety and tolerability of vortioxetine have been established in short- and long-term studies across the dose range of 5 to 20 mg/day. For information on undesirable effects, see section 4.8.
Vortioxetine did not increase the incidence of insomnia or somnolence relative to placebo.

In clinical short- and long-term placebo-controlled studies, potential discontinuation symptoms were systematically evaluated after abrupt treatment cessation of vortioxetine. There was no clinically relevant difference to placebo in the incidence or nature of the discontinuation symptoms after either short-term (6-12 weeks) or long-term (24-64 weeks) treatment with vortioxetine.

The incidence of self-reported adverse sexual reactions was low and similar to placebo in clinical short- and long-term studies with vortioxetine. In studies using the Arizona Sexual Experience Scale (ASEX), the incidence of treatment-emergent sexual dysfunction (TESD) and the ASEX total score showed no clinically relevant difference to placebo in symptoms of sexual dysfunction at the 5 to
15 mg/day doses of vortioxetine. For the 20 mg/day dose, an increase in TESD was seen compared to placebo (an incidence difference of 14.2%, 95% CI [1.4, 27.0]).

The effect of vortioxetine on sexual function was further evaluated in an 8-week, double-blind, flexible-dose, comparative study (n=424) versus escitalopram in patients treated for at least 6 weeks with an SSRI (citalopram, paroxetine, or sertraline), with a low level of depressive symptoms (baseline CGI-S ≤ 3) and TESD induced by the prior SSRI treatment. Vortioxetine
10-20 mg/day had statistically significantly less TESD than escitalopram 10-20 mg/day as measured by change in the CSFQ-14 total score (2.2 points, p=0.013) at week 8. The proportion of responders was not significantly different in the vortioxetine group (162 (74.7%)) compared with the escitalopram group (137 (66.2%)) at week 8 (OR 1.5 p=0.057). The antidepressant effect was maintained in both treatment groups.

Vortioxetine had no effect relative to placebo on body weight, heart rate, or blood pressure in clinical short- and long-term studies.

No clinically significant changes were observed in hepatic or renal assessments in clinical studies.

Vortioxetine has not shown any clinically significant effect on ECG parameters, including the QT, QTc, PR and QRS intervals, in patients with MDD. In a thorough QTc study in healthy subjects at doses up to 40 mg daily, no potential for the prolongation of the QTc interval was observed.

<u>Paediatric population</u>
Two short-term, randomised, double-blind, placebo-controlled, fixed-dose (vortioxetine 10 mg/day and 20 mg/day), active-referenced (fluoxetine), efficacy and safety studies have been conducted; one in children aged 7 to 11 years with MDD, and one in adolescents aged 12 to 17 years with MDD. The studies included a 4-week single-blind placebo lead-in period with standardized psychosocial intervention (treated patients in children study N=677, adolescent study N=777) and only non-responders from the lead-in period were randomised (children study N=540, adolescent study N=616).

In the study in children aged 7 to 11 years, the average effect of the two vortioxetine doses 10 and 20 mg/day was not statistically significantly different from placebo based on the Children´s Depression Rating Scale-Revised (CDRS-R) total score at week 8, nor was the active reference (fluoxetine 20 mg/day), nor did the individual vortioxetine doses (10 and 20 mg/day) show a nominally significant difference from placebo. In general, the adverse event profile of vortioxetine in children was similar to that seen for adults, except for higher incidence of abdominal pain reported in children.
Discontinuation due to adverse events was 2.0% in patients treated with vortioxetine 20 mg/day, 1.3% for vortioxetine
10 mg/day, 0.7% for placebo, and no discontinuations for fluoxetine. The most commonly reported adverse events in the vortioxetine treatment groups were nausea, headache, vomiting, dizziness, and abdominal pain. The incidence of nausea,

vomiting and abdominal pain was higher in the vortioxetine groups than in the placebo group. Suicidal ideation and behaviour were reported as adverse events during the 4-week single-blind lead-in period (placebo 2/677 [0.3%]), and during the 8-week treatment period (vortioxetine 10 mg/day 1/149 [0.7%], placebo 1/153 [0.7%]). In addition, the event 'non-specific active suicidal thoughts' was reported in the C-SSRS in 5 patients during the 8-week treatment period (vortioxetine 20 mg/day 1/153 [0.7%], placebo 1/153 [0.7%] and fluoxetine 3/82 [3.7%]). Suicidal ideation and behaviour as measured by Columbia-Suicide Severity Rating Scale (C-SSRS) was similar across treatment groups.

In the study in adolescents aged 12 to 17 years neither vortioxetine 10 mg/day nor 20 mg/day was statistically significantly superior to placebo based on the Children´s Depression Rating Scale-Revised (CDRS-R) total score. The active reference (fluoxetine 20 mg/day) separated statistically from placebo on the CDRS-R total score. 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 and suicidal ideation. Discontinuation due to adverse events (mostly due to suicidal ideation, nausea and vomiting) was highest in patients treated with vortioxetine 20 mg/day (5.6%) as compared to vortioxetine 10 mg/day (2.7%), fluoxetine (3.3%), and placebo (1.3%). The most commonly reported adverse events in the vortioxetine treatment groups were nausea, vomiting and headache. Suicidal ideation and behaviour were reported as adverse events both during the 4-week single-blind lead-in period (placebo 13/777 [1.7%]), and during the 8-week treatment period (vortioxetine 10 mg/day 2/147 [1.4%], vortioxetine 20 mg/day 6/161 [3.7%], fluoxetine 6/153 [3.9%], placebo 0/154 [0%]). Suicidal ideation and behaviour as measured by C-SSRS was similar across treatment groups.

Vortioxetine should not be used in paediatric patients (under 18 years of age) with major depressive disorder (see section 4.2). The European Medicines Agency has waived the obligation to submit the results of studies in major depressive disorder with the reference medicinal product containing vortioxetine in children aged less than 7 years (see section 4.2 for information on paediatric use).

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% (C_{max} and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10 mg/day. The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years (see section 4.2). However, caution should be exercised when prescribing to elderly patients at doses higher than 10 mg vortioxetine once daily (see section 4.4).

Renal impairment
Following a single dose of 10 mg vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, or severe; n=8 per group) caused modest exposure increases (up to 30%), compared to healthy matched controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during dialysis (AUC and C_{max} were 13% and 27% lower, respectively; n=8) following a single 10 mg dose of vortioxetine. No dose adjustment is needed based on renal function (see section 4.2 and 4.4).

Hepatic impairment
The pharmacokinetics in subjects (N = 6-8) with mild, moderate, or severe hepatic impairment (Child- Pugh Criteria A, B, or C, respectively) were compared to healthy volunteers. The changes in AUC were less than 10% lower in subjects with mild or moderate hepatic impairment, and 10% higher in those with severe hepatic impairment. The changes in 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 two efficacy and safety studies (7-17 years). The pharmacokinetics of vortioxetine in paediatric patients was similar to that observed in adult patients.

5.3 Preclinical safety data

Administration of vortioxetine in the general toxicity studies in mice, rats and dogs was mainly associated with CNS-related clinical signs. These included salivation (rat and dog), pupil dilatation (dog), and two incidences of convulsions in dogs in the general toxicity study programme. A no-effect level for convulsions was established with a corresponding safety margin of 5 considering the maximum recommended therapeutic dose of 20 mg/day. Target organ toxicity was restricted to kidneys (rats) and liver (mice and rats). The changes in the kidney in rats (glomerulonephritis, renal tubular obstruction, crystalline material in renal tubule) and in the liver of mice and rats (hepatocellular hypertrophy, hepatocyte necrosis, bile duct hyperplasia, crystalline material in bile ducts) were seen at exposures more than 10-fold (mice) and 2-fold (rats) the human exposure at the maximum recommended therapeutic dose of 20 mg/day. These findings were mainly attributed to rodent-specific vortioxetine-related crystalline material obstruction of the renal tubules and the bile ducts, respectively, and considered of low risk to humans.

Vortioxetine was not genotoxic in a standard battery of in vitro and in vivo tests.

Based on results from conventional 2-year carcinogenicity studies in mice or rats, vortioxetine is not considered to pose a risk of carcinogenicity in humans.

Vortioxetine had no effect on rat fertility, mating performance, reproductive organs, or sperm morphology and motility. Vortioxetine was not teratogenic in rats or rabbits, but reproductive toxicity in terms of effects on foetal weight and delayed ossification were seen in the rat at exposures more than 10-fold the human exposure at the maximum recommended therapeutic dose of 20 mg/day.
Similar effects were seen in the rabbit at sub-therapeutic exposure.

In a pre- and post-natal study in rats, vortioxetine was associated with increased pup mortality, reduced bodyweight gain, and delayed pup development at doses that did not result in maternal toxicity and with associated exposures similar to those achieved in humans following administration of vortioxetine 20 mg/day (see section 4.6).

Vortioxetine-related material was distributed to the milk of lactating rats (see section 4.6).
In juvenile toxicity studies in rats, all vortioxetine treatment-related findings were consistent with those noted in adult animals.

Environmental risk assessment studies have shown that vortioxetine has the potential to be persistent, bioaccumulative and toxic to the environment (risk to fish). However, by recommended patient usage vortioxetine is considered to pose negligible risk to the aquatic and terrestrial environment (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Cellulose, microcrystalline
Sodium starch glycolate
Hydroxypropylcellulose
Magnesium stearate (E470b)

Film coating
Hypromellose
Macrogol
Titanium dioxide (E171)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Non perforated, calendar pack blister or perforated blister (PVC/PVDC//Al): 14, 28 and 98 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/121/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th August 2025

10 DATE OF REVISION OF THE TEXT