Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Vorto (vortioxetine hydrobromide) 10mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains:
Vortioxetine Hydrobromide
Eq. to Vortioxetine..... 10 mg

Excipients with known effects
Colour: Sunset yellow

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablets

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The starting and recommended dose 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 dose reduction.

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.

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.

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.

Paediatric population
The safety and efficacy of Brintellix in children and adolescents under 18 years have not been established. No data are available.

Method of administration
For oral use.
The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Concomitant use with nonselective monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors

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, 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 before 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.
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, unco-ordination), 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.

Hemorrhage
Bleeding abnormalities, such as ecchymoses, purpura, and other hemorrhagic events, such as gastrointestinal or gynecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effects (SSRIs, SNRIs). 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) 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 medications known to cause hyponatremia.
Discontinuation of vortioxetine should be considered in patients with symptomatic hyponatraemia, and appropriate medical intervention should be instituted.

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.

Renal impairment

Limited data are available for patients with severe renal impairment. Caution should therefore be exercised.

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 by CYP3A4/5 and CYP2C9.

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.

Reversible, selective MAO-A inhibitor (moclobemide)

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

Reversible, non-selective MAOI (linezolid)

The combination of vortioxetine with a weak reversible and non-selective MAOI, such as the antibiotic linezolid, is contraindicated. If the combination proves necessary, the added medicinal product should be given with a minimum dosage and under close clinical monitoring for serotonin syndrome.

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.

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.

St. John's wort
Concomitant use of antidepressants with serotonergic effects and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in a higher incidence of adverse reactions, including Serotonin Syndrome.

Medicinal products lowering the seizure threshold.
Antidepressants with serotonergic effects 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].

CYP2D6 inhibitors
The exposure to vortioxetine increased 2.3-fold for the 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 a strong CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment.

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.

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

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
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.

Cytochrome P450 substrates
In vitro, vortioxetine did not show any relevant potential for inhibition or induction of cytochrome P450 isozymes.
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).

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 Pregnancy and Lactation

Pregnancy

If a woman decides to become pregnant, the use of vortioxetine should be carefully re-evaluated.

Studies in animals have shown reproductive toxicity.

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 not be used during pregnancy unless the clinical condition of the woman requires treatment with vortioxetine.

Breastfeeding mothers

Available data in animals have shown excretion of vortioxetine/ vortioxetine metabolites in milk. It is expected that vortioxetine will be excreted into human milk. Therefore, a risk to the suckling 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 studies

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

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 the ability to drive and use machines

It 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. 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. Gastrointestinal adverse reactions, such as nausea, occurred more frequently in women than men.

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).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Common	Abnormal dreams
	Uncommon	Bruxism
Nervous system disorders	Common	Dizziness
Vascular disorders	Uncommon	Flushing
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Generalised pruritus
	Uncommon	Night sweats

Description of selected adverse reactions

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).

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 from placebo. However, the 20 mg dose of
9 vortioxetine was associated with an increase in treatment-emergent sexual dysfunction (TESD)
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 drug 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.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

There is limited experience with vortioxetine overdose.
Ingestion of vortioxetine in the dose range of 40 to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.
Management of overdose should consist of treating clinical symptoms and relevant monitoring.
Medical follow-up in a specialised environment is recommended.

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-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin but probably also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems. 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 humans.
In humans, two positron emission tomography (PET) studies have been conducted using 5-HT transporter ligands (11C-MADAM or 11C-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.

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 Cmax values of 9 to 33 ng/mL were observed. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution

The mean volume of distribution (Vss) is 2,600 L, indicating extensive extravascular distribution. Vortioxetine is highly bound to plasma proteins (98 to 99%) and the binding appears to be independent of vortioxetine plasma concentrations.

Biotransformation

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9, and subsequent glucuronic acid
conjugation.
No inhibitory or inducing effect of vortioxetine was observed in the drug-drug interaction studies 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 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.

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 the 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 were 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 did not affect 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 was 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).
Vortioxetine-related material was distributed in the milk of lactating rats.
In juvenile toxicity studies in rats, all vortioxetine treatment-related findings were consistent with those noted in adult animals.
The active ingredient vortioxetine hydrobromide is currently considered hazardous (persistent, bioaccumulative, and toxic; risk to fish) for the environment.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose
Starch
Lactose
Sodium starch glycolate
PVPK 30
Isopropyl alcohol
Magnesium stearate
Talc
Cross povidone
Colloidal silicon dioxide
Yellow oxide of iron

MDC

6.2 Incompatibilities
None.

6.3 Shelf-Life
36 months (3 years)

6.4 Special Precautions for Storage
Do not store above 30°C.
Keep out of reach of children.

6.5 Nature and Content of Container
30 Tablets in an Alu/ Alu. Each Blister in a Printed carton box with pack insert.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of per local requirements.

7. Marketing Authorization Holder
REDEFINE HEALTHCARE LIMITED

P.O. BOX 1907-00606, NAIROBI, KENYA

8. Marketing Authorization Number
CTD11813

9. Date of first authorization/renewal of the authorization
17/01/2025

10. Date of revision of the text
6/05/2025