

Product Information

Brintellix oral drops

Vortioxetine (as (D,L)-lactate)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix oral drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains vortioxetine (D,L)-lactate equivalent to 20 mg vortioxetine.

Each drop contains vortioxetine (D,L)-lactate equivalent to 1 mg vortioxetine.

Excipients with known effect

Each drop contains 4.25 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution.

Clear, nearly colourless to yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Brintellix 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 Brintellix 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.

5 mg corresponding to 5 drops.

10 mg corresponding to 10 drops.

15 mg corresponding to 15 drops.

20 mg corresponding to 20 drops.

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 Brintellix in children aged 7 to 11 years have not been established. No data are available (see section 4.4). Brintellix 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 Brintellix 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).

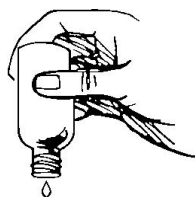
Method of administration

Brintellix is for oral use.

The oral drops can be taken with or without food.

The drops can be mixed with water, juice or other non-alcoholic drinks.

The bottle must be turned completely upside down. If no drops come out, the bottle can be tapped lightly to start the flow.



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

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

Renal impairment

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

Hepatic impairment

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

Excipient contents

This medicinal product contains 85 mg of alcohol (ethanol 96%) in each ml which is equivalent to 10.1 % v/v.

4.5 Interaction with other medicinal products and other forms of interaction

Vortioxetine is extensively metabolised in the liver, primarily through oxidation and subsequent glucuronic acid conjugation. In vitro, the cytochrome P450 isoenzyme CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine (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.

Cytochrome P450 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 a strong CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment (see section 4.2).

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.

Co-administration of strong inhibitors of CYP3A4 and CYP2C9 to CYP2D6 poor metabolisers has not been investigated specifically, but it is anticipated that it will lead to increased exposure of vortioxetine in these patients (see section 5.2). 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.

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).

Potential pharmacokinetic interactions

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.

Animal studies did not demonstrate a teratogenic effect of vortioxetine, but effects on foetal weight and delayed ossification were seen (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).

Brintellix 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 Brintellix 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).

4.7 Effects on ability to drive and use machines

No significant impairment, relative to placebo, in driving performance, cognitive function or other psychomotor skills (using a battery of neuropsychological tests) was observed when healthy subjects were administered single and multiple doses of 10 mg/day vortioxetine. However, as adverse reactions such as dizziness have been reported, patients should exercise caution when driving or operating hazardous machinery.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
	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.

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. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system to Health Product Vigilance Center (HPVC), Food and Drug Administration Thailand: Tel. 02-590-7288 or <http://www.fda.moph.go.th/vigilance> or adr@fda.moph.go.th

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: 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-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 the serotonin, 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. In addition, a nonclinical behavioural study in male animals indicates that vortioxetine does not induce sexual dysfunction. 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 (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 specific regions of interest was approximately 50% at 5 mg/day, 65% at 10 mg/day and increased to above 80% at 20 mg/day. Vortioxetine has shown clinical antidepressant effects at 5-HT transporter occupancies as low as 50%.

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 in major depressive disorder (MDD). Twelve double-blind, placebo-controlled, 6/8-week, fixed-dose studies; 11492A, 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, 317, 12541A have been conducted to investigate the short-term efficacy of vortioxetine in MDD both in adults and in the elderly. The efficacy of vortioxetine was demonstrated across 9 of the 12 studies, as measured by improvement in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D₂₄) total score, and 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. 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) and on the anxiety symptoms in depression (assessed using the HAM-A total score).

Maintenance

The maintenance of antidepressant efficacy was demonstrated in a relapse-prevention study 11985A. 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 12541A in elderly depressed patients (aged ≥65 years,), vortioxetine 5 mg/day was superior to placebo as measured by improvement in the

MADRS and HAM-D₂₄ total scores. In the dose range of 5 to 20mg/day vortioxetine, efficacy and tolerability in the elderly was in line with the results in the adult population.

Patients with severe depression or with depression and high levels of anxiety symptoms

Antidepressant efficacy was also demonstrated 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) in short-term studies including the study 12541A in the elderly and in the long-term relapse-prevention study 11985A.

Patients with inadequate response to SSRI/SNRI treatment

In a 12-week, double-blind, flexible-dose, comparative study 14178A in patients with moderate to severe depression who switched antidepressant treatment after an inadequate response to an SSRI/SNRI for the current episode vortioxetine 10-20 mg/day was statistically significantly better than agomelatine 25-50 mg/day as measured by improvement in the MADRS total score. The clinical relevance was supported by the proportion of remitters and improvement in CGI-I and Sheehan Disability Scale (SDS) scores).

Cognitive dysfunction in depression

In a short-term study 12541A in MDD in the elderly (≥ 65 years of age), vortioxetine (5 mg/day) demonstrated positive effects relative to placebo on a neuropsychological test of executive function, processing speed, and attention, the Digit Symbol Substitution Test (DSST), and on a test of learning and memory, the Rey Auditory Verbal Learning Test (RAVLT), whereas the active reference duloxetine separated from placebo on the RAVLT only.

Further, vortioxetine was superior to placebo in a range of neuropsychological tests involving the above-mentioned cognitive processes in study 14122A in MDD in adults (< 65 years of age). Vortioxetine (10 and 20 mg/day) was superior to placebo on the primary outcome measure, a composite cognition score comprising the two neuropsychological tests, the DSST and the RAVLT. An improved performance was seen across all secondary measures of cognitive performance and on a patient-reported outcome of cognitive function.

In both studies; 12541A and 14122A the effect of vortioxetine was mainly an independent effect on cognitive performance rather than an indirect effect through improvement of depressive symptoms.

Health-related quality of life and overall functioning

Vortioxetine was superior to placebo in health-related quality of life, as assessed using the SF-36 Mental Component Summary and the Quality of Life Enjoyment Satisfaction Questionnaire total and life satisfaction scores. This was supported by clinically relevant improvements in the overall health rating as measured using EQ-5D (EuroQol index) and in the overall functioning as assessed using the Sheehan Disability Scale (SDS) total score in the areas of work, social life, and family life versus placebo or an active comparator (agomelatine). Furthermore, the superior effects relative to placebo in health related quality of life were maintained in the long-term relapse prevention study.

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 significant difference to placebo in symptoms of sexual dysfunction for doses 5-20mg/day, however higher doses were associated with a numerical increase in TESD.

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 $\leq$ 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.

Paediatric population

One randomised, double-blind, placebo-controlled, active-referenced, fixed dose, 8-week study was conducted in adolescent patients with MDD aged 12 to 17 years. The study included a 4-week single-blind placebo lead-in period with standardized psychosocial intervention (N=777); only non-responders from the lead-in period were randomised (N=615). 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 adolescent than in adults for abdominal pain-related event 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 Columbia-Suicide Severity Rating Scale (C-SSRS) was similar across treatment groups.

The European Medicines Agency has waived the obligation to submit the results of studies in major depressive disorder with vortioxetine in children aged less than 7 years (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with vortioxetine in one or more subsets of the paediatric population in treatment of major depressive disorder (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 and subsequent glucuronic acid conjugation.

In vitro, the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6 are involved in the metabolism of vortioxetine.

No inhibitory or inducing effect of vortioxetine was observed in vitro for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5. Vortioxetine is a poor P-gp substrate and inhibitor.

The major metabolite of vortioxetine is pharmacologically inactive.

Elimination

The mean elimination half-life and oral clearance are 66 hours and 33 L/h, respectively. Approximately 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. No dose adjustment is needed (see section 4.2).

Renal impairment

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

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 poor metabolisers

The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. In the presence of strong CYP3A4/2C9-inhibitors, the exposure could potentially be high (see section 4.5).

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

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 one episode of convulsions in each of two dogs. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex
Ethanol (96 per cent)
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

After opening the drops should be used within 8 weeks.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

15 ml in an amber glass bottle (type III) and screw cap (polypropylene) with dropper (LD-polyethylene), (child-resistant closure).
Pack of 1 glass bottle.

6.6 Special precautions for disposal

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

7. MANUFACTURER

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Ottiliavej 9
2500 Valby
Denmark

Representative Offices

Thailand
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Bangkok, Thailand.

8. DATE OF REVISION OF THE TEXT

| October 2021