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).

Brintellix should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.

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).
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

Brintellix 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
Metabolism and nutrition disorders	Not known *	Hyponatraemia
Psychiatric disorders	Common	Abnormal dreams
Nervous system disorders	Common	Dizziness
	Not known *	Serotonin Syndrome
Vascular disorders	Uncommon	Flushing
	Not known*	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus, including pruritus generalised
	Uncommon	Night sweats
	Not known*	Angioedema, Urticaria Rash

* Based on post-marketing cases

Description of selected adverse reactions

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

Elderly patients
For doses ≥10 mg vortioxetine once daily, the withdrawal rate from the studies was higher in patients aged ≥65 years.
For doses of 20 mg vortioxetine once daily, the incidences of nausea and constipation were higher in patients aged ≥65 years (42% and 15%, respectively) than in patients aged <65 years (27% and 4%, respectively)(see section 4.4).

Sexual dysfunction
In clinical studies, sexual dysfunction was assessed using the Arizona Sexual Experience Scale (ASEX). Doses of 5 to 15 mg showed no difference to placebo. However, the 20 mg dose of vortioxetine was associated with an increase in sexual dysfunction (TESD)(see section 5.1) .

Class effect
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving a medicinal product from related pharmacological classes of antidepressants (SSRIs or TCAs). The mechanism behind this risk is unknown, and it is not known if this risk is also relevant for vortioxetine.

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 listed in Appendix V

4.9 Overdose

Ingestion of vortioxetine in clinical trials in the dose range of 40 mg to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience mainly concerns vortioxetine overdoses of up to 80 mg. In the majority of cases, no symptoms or mild symptoms were reported. The most frequently reported symptoms were nausea and vomiting.

There is limited experience with vortioxetine overdoses above 80 mg. Following dosages several fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported.

Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants, ATC code: N06AX26

Mechanism of action

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Nonclinical data indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 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 nucle*i 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 $\Delta = 1.75$ ($p = 0.019$) to 4.26 ($p < 0.0001$) in the 2 studies in adults and $\Delta = 2.79$ ($p = 0.023$) 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]).

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
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 in major depressive disorder with vortioxetine in children and adolescents aged 7 to 18 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 (see section 4.4).

Hepatic impairment
Following a single dose of 10 mg vortioxetine, no impact of mild or moderate hepatic impairment (Child-Pugh Criteria A or B; n=8 per group) was observed on the pharmacokinetics of vortioxetine (changes in AUC were less than 10%). No dose adjustment is needed (see section 4.2). Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients (see section 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).

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

Brintellix 5 mg film-coated tablets

Tablet core

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycolate (type A)
Magnesium stearate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide red (E172)

Brintellix 10 mg film-coated tablets

Tablet core

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycolate (type A)
Magnesium stearate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)

Brintellix 15 mg film-coated tablets

Tablet core

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycolate (type A)
Magnesium stearate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)

Brintellix 20 mg film-coated tablets
Tablet core

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Sodium starch glycolate (type A)
Magnesium stearate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Brintellix 5 mg film-coated tablets

Blister: Transparent; PVC/PVdC/aluminium blister.
Pack sizes of 14, 28 and 98 film-coated tablets.

Perforated unit dose blisters: PVC/PVdC/aluminium.
Pack sizes of 56 x 1 and 98 x 1 film-coated tablets.
Multipack containing 126 (9 x 14) and 490 (5 x (98x1)) film-coated tablets.

High-density polyethylene (HDPE) tablet container.
Pack sizes of 100 and 200 film-coated tablets.

Brintellix 10 mg film-coated tablets
Blister: Transparent; PVC/PVdC/aluminium blister.
Pack sizes of 7, 14, 28, 56 and 98 film-coated tablets.

Perforated unit dose blisters: PVC/PVdC/aluminium.
Pack sizes of 56 x 1 and 98 x 1 film-coated tablets.
Multipack containing 126 (9 x 14) and 490 (5 x (98x1)) film-coated tablets.

High-density polyethylene (HDPE) tablet container.
Pack sizes of 100 and 200 film-coated tablets.

Brintellix 15 mg film-coated tablets
Blister: Transparent; PVC/PVdC/aluminium blister.
Pack sizes of 14, 28, 56 and 98 film-coated tablets.

Perforated unit dose blisters: PVC/PVdC/aluminium.
Pack sizes of 56 x 1 and 98 x 1 film-coated tablets.
Multipack containing 490 (5 x (98x1)) film-coated tablets.

High-density polyethylene (HDPE) tablet container.
Pack sizes of 100 and 200 film-coated tablets.

Brintellix 20 mg film-coated tablets
Blister: Transparent; PVC/PVdC/aluminium blister.
Pack sizes of 14, 28, 56 and 98 film-coated tablets.

Perforated unit dose blisters: PVC/PVdC/aluminium.
Pack sizes of 56 x 1 and 98 x 1 film-coated tablets.
Multipack containing 126 (9 x 14) and 490 (5 x (98x1)) film-coated tablets.

High-density polyethylene (HDPE) tablet container.
Pack sizes of 100 and 200 film-coated tablets.

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

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

Brintellix 5 mg film-coated tablets

EU/1/13/891/001-007
EU/1/13/891/037-038

Brintellix 10 mg film-coated tablets

EU/1/13/891/008-017
EU/1/13/891/039

Brintellix 15 mg film-coated tablets

EU/1/13/891/018-026

Brintellix 20 mg film-coated tablets

EU/1/13/891/027-035
EU/1/13/891/040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2013
Date of latest renewal: 20 November 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg/ml oral drops, solution

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).

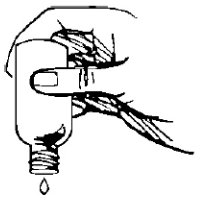
Cytochrome P450 inducers
Depending on individual patient response, a dose adjustment of vortioxetine may be considered if a broad cytochrome P450 inducer (e.g., rifampicin, carbamazepine, phenytoin) is added to vortioxetine treatment (see section 4.5).

Paediatric population
The safety and efficacy of Brintellix in children and adolescents aged less than 18 years have not been established. No data are available (see section 4.4).

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 patients aged less than 18 years since the safety and efficacy of vortioxetine have not been established in this age group (see section 4.2). In clinical studies in children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, 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 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.

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 . 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.

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

Hepatic impairment

Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients (see section 5.2).

Ethanol

This medicinal product contains small amounts of ethanol, less than 100 mg per dose.

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., tramadol, sumatriptan and other triptans*)* may lead to Serotonin Syndrome (see section 4.4).

St. John's wort
Concomitant use of antidepressants with serotonergic effect and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in a higher incidence of adverse reactions including Serotonin Syndrome (see section 4.4).

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

ECT (electroconvulsive therapy)
There is no clinical experience with concurrent administration of vortioxetine and ECT, therefore caution is advisable.

CYP2D6 inhibitors
The exposure to vortioxetine increased 2.3-fold for area under the curve (AUC) when vortioxetine 10 mg/day was co-administered with bupropion (a strong CYP2D6 inhibitor 150 mg twice daily) for 14 days in healthy subjects. Co-administration resulted in a higher incidence of adverse reactions when bupropion was added to vortioxetine than when vortioxetine was added to bupropion. Depending on individual patient response, a lower dose of vortioxetine may be considered if a 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 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.

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).

Brintellix should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.

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).
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

Brintellix has no or negligible influence on the ability to drive and use machines. However, as adverse reactions such as diziness 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
Metabolism and nutrition disorders	Not known *	Hyponatraemia
Psychiatric disorders	Common	Abnormal dreams
Nervous system disorders	Common	Dizziness
	Not known *	Serotonin Syndrome
Vascular disorders	Uncommon	Flushing
	Not known *	Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus, including pruritus generalised
	Uncommon	Night sweats
	Not known*	Angioedema, Urticaria Rash

* Based on post-marketing cases

Description of selected adverse reactions

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

Elderly patients
For doses ≥10 mg vortioxetine once daily, the withdrawal rate from the studies was higher in patients aged ≥65 years.
For doses of 20 mg vortioxetine once daily, the incidences of nausea and constipation were higher in patients aged ≥65 years (42% and 15%, respectively) than in patients aged <65 years (27% and 4%, respectively)(see section 4.4).

Sexual dysfunction
In clinical studies, sexual dysfunction was assessed using the Arizona Sexual Experience Scale (ASEX). Doses of 5 to 15 mg showed no difference to placebo. However, the 20 mg dose of vortioxetine was associated with an increase in sexual dysfunction (TESD)(see section 5.1) .

Class effect
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving a medicinal productfrom 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

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 listed in Appendix V

4.9 Overdose

Ingestion of vortioxetine in clinical trials in the dose range of 40 mg to 75 mg has caused an aggravation of the following adverse reactions: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalised pruritus, somnolence and flushing.

Post-marketing experience mainly concerns vortioxetine overdoses of up to 80 mg. In the majority of cases, no symptoms or mild symptoms were reported. The most frequently reported symptoms were nausea and vomiting.

There is limited experience with vortioxetine overdoses above 80 mg. Following dosages several fold higher than the therapeutic dose range, events of seizure and serotonin syndrome have been reported.

Management of overdose should consist of treating clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants, ATC-code: N06AX26

Mechanism of action

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Nonclinical data indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 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 nucle*i 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 15mg/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 $\Delta = 1.75$ ($p = 0.019$) to 4.26 ($p < 0.0001$) in the 2 studies in adults and $\Delta = 2.79$ ($p = 0.023$) 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]).

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
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 in major depressive disorder with vortioxetine in children and adolescents aged 7 to 18 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 CYP2C9and 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 of age (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 (see section 4.4).

Hepatic impairment
Following a single dose of 10 mg vortioxetine, no impact of mild or moderate hepatic impairment (Child-Pugh Criteria A or B; n=8 per group) was observed on the pharmacokinetics of vortioxetine (changes in AUC were less than 10%). No dose adjustment is needed (see section 4.2). Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients (see section 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).

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 pesistent, 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

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

This medicinal product does not require any special storage conditions.

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. MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2013
Date of latest renewal: 20 November 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
DENMARK

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR THE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 5 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
98 film-coated tablets
56x1 film-coated tablets
98x1 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/001 14 film-coated tablets
EU/1/13/891/002 28 film-coated tablets
EU/1/13/891/003 56 x 1 film-coated tablets
EU/1/13/891/004 98 x 1 film-coated tablets
EU/1/13/891/006 100 film-coated tablets
EU/1/13/891/007 200 film-coated tablets
EU/1/13/891/037 98 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 5 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets.
98 x 1 film-coated tablets.
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/038 126 film-coated tablets (9 packs of 14)
EU/1/13/891/005 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 5 mg film-coated tablets
Vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 126 (9 packs of 14) film-coated tablets.
Multipack: 490 (5 packs of 98 x 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/038 126 film-coated tablets (9 packs of 14)
EU/1/13/891/005 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 5 mg tablet
vortioxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S

3. EXPIRY DATE

EXP (MM-YYYY)
See embossed stamp.

4. BATCH NUMBER

Lot
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR THE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 10 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablets
98 film-coated tablets
98 x 1 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/008 7 film-coated tablets
EU/1/13/891/009 14 film-coated
EU/1/13/891/010 28 film-coated tablets
EU/1/13/891/011 56 film-coated tablets
EU/1/13/891/012 98 film-coated tablets
EU/1/13/891/013 56x1 film-coated tablets
EU/1/13/891/014 98x1 film-coated tablets
EU/1/13/891/016 100 film-coated tablets
EU/1/13/891/017 200 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 10 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
98 x 1 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/039 126 film-coated tablets (9 packs of 14)
EU/1/13/891/015 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 10 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 126 (9 packs of 14) film-coated tablets.
Multipacks: 490 (5 packs of 98 x 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/039 126 film-coated tablets (9 packs of 14)
EU/1/13/891/015 490 film-coated tablets (5 packs of 98x1).

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 10 mg tablet
vortioxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S

3. EXPIRY DATE

EXP (MM-YYYY)
See embossed stamp.

4. BATCH NUMBER

Lot
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR THE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 15 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablets
98 film-coated tablets
98 x 1 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/018 14 film-coated tablets
EU/1/13/891/019 28 film-coated tablets
EU/1/13/891/020 56 film-coated tablets
EU/1/13/891/021 98 film-coated tablets
EU/1/13/891/022 56x1 film-coated tablets
EU/1/13/891/023 98x1 film-coated tablets
EU/1/13/891/025 100 film-coated tablets
EU/1/13/891/026 200 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 15 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 x 1 film-coated tablets.
Component of a multipack, can't be sold seperatly.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/024 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 15 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 490 (5 packs of 98x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/024 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 15 mg tablet
vortioxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S

3. EXPIRY DATE

EXP (MM-YYYY)
See embossed stamp.

4. BATCH NUMBER

Lot
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR THE TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablets
98 film-coated tablets
98 x 1 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/027 14 film-coated tablets
EU/1/13/891/028 28 film-coated tablets
EU/1/13/891/029 56 film-coated tablets
EU/1/13/891/030 98 film-coated tablets
EU/1/13/891/031 56x1 film-coated tablets
EU/1/13/891/032 98x1 film-coated tablets
EU/1/13/891/034 100 film-coated tablets
EU/1/13/891/035 200 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg film-coated tablets
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
98 x 1 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/040 126 film-coated tablets (9 packs of 14)
EU/1/13/891/033 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg film-coated tablets
Vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg vortioxetine (as hydrobromide)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 126 (9 packs of 14) film-coated tablets.
Multipack: 490 (5 packs of 98x1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/040 126 film-coated tablets (9 packs of 14)
EU/1/13/891/033 490 film-coated tablets (5 packs of 98x1)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg tablet
vortioxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S

3. EXPIRY DATE

EXP (MM-YYYY)
See embossed stamp.

4. BATCH NUMBER

Lot
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Brintellix 20 mg/ml oral drops, solution
vortioxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each drop contains 1 mg vortioxetine (as (D,L)- lactate)

3. LIST OF EXCIPIENTS

Contains ethanol

4. PHARMACEUTICAL FORM AND CONTENTS

oral drops, solution
15 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

[outer carton only]:
Turn the bottle completely upside down. If no drops come out, tap the bottle lightly to start the flow.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM-YYYY}
When opened, use within 8 weeks

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/891/036 15 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brintellix 20 mg/ml [outer carton only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. [outer carton only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

[outer carton only]
PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Brintellix 5 mg film-coated tablets
vortioxetine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Brintellix is and what it is used for
2. What you need to know before you take Brintellix
3. How to take Brintellix
4. Possible side effects
5. How to store Brintellix
6. Contents of the pack and other information

1. What Brintellix is and what it is used for

Brintellix contains the active substance vortioxetine. It belongs to a group of medicines called antidepressants.

Brintellix is used to treat major depressive episodes in adults.

Brintellix has been shown to reduce the broad range of depressive symptoms, including sadness, inner tension (feeling anxious), sleep disturbances (reduced sleep), reduced appetite, difficulty in concentrating, feelings of worthlessness, loss of interest in favourite activities, feeling of being slowed down.

2. What you need to know before you take Brintellix

Do not take Brintellix:

- if you are allergic to vortioxetine or any of the other ingredients of this medicine (listed in section 6).
- if you are taking other medicines for depression known as non-selective monoamine oxidase inhibitors or selective MAO-A inhibitors. Ask your doctor if you are uncertain.

Warnings and precautions

Talk to your doctor or pharmacist before taking Brintellix if you:

- are taking medicines with a so-called serotonergic effect, such as:
  - tramadol (a strong painkiller).
  - sumatriptan and similar medicines with active substance names ending in “triptans” (used to treat migraine).

Taking these medicines together with Brintellix may increase the risk of serotonin syndrome. This syndrome may be associated with hallucinations, involuntary twitching, accelerated heartbeat, high blood pressure, fever, nausea and diarrhoea.

- have had fits (seizures).
  Your doctor will treat you cautiously if you have a history of fits or have unstable fit disorders/epilepsy. Fits are a potential risk with medicines used to treat depression. Treatment should be discontinued in any patient who develops fits or where there is an increase in the frequency of fits.

- have had mania
- have a tendency to bleed or bruise easily.
- have low sodium level in the blood.
- are 65 years of age or older.
- have a severe kidney disease.
- have a severe liver disease or a liver disease called cirrhosis.

Thoughts of suicide and worsening of your depression

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this if you:
- have previously had thoughts about killing or harming yourself.
- are a young adult.

Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Children and adolescents

Brintellix is not recommended in children and adolescents under 18 years due to lack of information for this age group.

Other medicines and Brintellix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:

- phenelzine, iproniazid, isocarboxazid, nialamide, tranylcypromine (medicines to treat depression called non-selective monoamine oxidase inhibitors); you must not take any of these medicines together with Brintellix. If you have taken any of these medicines, you will need to wait 14 days before you start taking Brintellix. After stopping Brintellix you must allow 14 days before taking any of these medicines.
- moclobemide (a medicine to treat depression).
- selegiline, rasagiline (medicines to treat Parkinson's disease).
- linezolid (a medicine to treat bacterial infections).
- lithium (a medicine to treat depression and mental disorders) or tryptophan.
- medicines know to cause low sodium level.

- rifampicin (a medicine to treat tuberculosis and other infections).
- carbamazepine, phenytoin (medicines to treat epilepsy or other illness).
- warfarin, dipyridamole, phenprocoumon, low-dose acetylsalicylic acid (blood thinning medicines).

Medicines that increase the risk of fits:
- sumatriptan and similar medicines with active substance names ending in “triptans”.
- tramadol (a strong painkiller).
- mefloquine (a medicine to prevent and treat malaria).
- bupropion (a medicine to treat depression also used to wean from smoking).
- fluoxetine, paroxetine and other medicines to treat depression called SSRI/SNRIs, tricyclics.
- St John’s wort (hypericum perforatum) (a medicine to treat depression).
- quinidine (a medicine to treat heart rhythm disorders).
- chlorpromazine, chlorprothixene, haloperidol (medicines to treat mental disorders belonging to the groups called phenothiazines, thioxanthenes, butyrophenones).

Please tell your doctor if you are taking any of the medicines above, since your doctor needs to know if you already are at risk for seizures.

Brintellix with alcohol

Combining this medicine with alcohol is not advisable.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

Brintellix should not be used during pregnancy unless the doctor says it is absolutely necessary.

If you take medicines to treat depression, including Brintellix, during the last 3 months of your pregnancy, you should be aware that the following effects may be seen in your newborn baby: trouble with breathing, bluish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. Contact your doctor immediately if your newborn baby has any of these symptoms.

Make sure your midwife and/or doctor know you are on Brintellix. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Brintellix may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.

Breast-feeding

It is expected that the ingredients of Brintellix will pass into breast milk. Brintellix is not to be used during breast-feeding. Your doctor will make a decision on whether you should stop breast-feeding, or stop using Brintellix taking into account the benefit of breast-feeding for your child, and the benefit of therapy for you.

Driving and using machines

Brintellix has no or negligible influence on the ability to drive and use machines. However, as adverse reactions such as diziness have been reported, caution is advised during such activities when beginning Brintellix treatment or changing the dose.

3. How to take Brintellix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Brintellix is 10 mg vortioxetine taken as one daily dose in adults less than 65 years of age. The dose may be increased by your doctor to a maximum of 20 mg vortioxetine per day or lowered to a minimum of 5 mg vortioxetine per day depending on your response to treatment.

For elderly people 65 years of age or older, the starting dose is 5 mg vortioxetine taken once daily.

Method of administration

Take one tablet with a glass of water.
The tablet can be taken with or without food.

Duration of treatment

Take Brintellix for as long as your doctor recommends.

Continue to take Brintellix even if it takes some time before you feel any improvement in your condition.

Treatment should be continued for at least 6 months after you feel well again.

If you take more Brintellix than you should

If you take more than the prescribed dose of Brintellix, contact your doctor or nearest hospital emergency department immediately. Have the container and any remaining tablets available. Do this even if there are no signs of discomfort. Overdose signs are dizziness, nausea, diarrhoea, stomach discomfort, itching of the whole body, sleepiness and flushing.

Following intake of dosages several times higher than the prescribed dose, fits (seizures) and a rare condition called serotonin syndrome have been reported.

If you forget to take Brintellix

Take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Brintellix

Do not stop taking Brintellix without talking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects were mild to moderate and occurred within the first two weeks of treatment. The reactions were usually temporary and did not lead to cessation of therapy.

Side effects listed below have been reported in the following frequencies.

Very common: may affect more than 1 in 10 people
- nausea

Common: may affect up to 1 in 10 people
- diarrhoea, constipation, vomiting
- dizziness
- itching of the whole body
- abnormal dreams

Uncommon: may affect up to 1 in 100 people
- flushing
- night sweats

Not known: frequency cannot be estimated from available data
- low levels of sodium in the blood (the symptoms may include feeling dizzy, weak, confused, sleepy or very tired, or feeling or being sick; more serious symptoms are fainting, fits or falls)
- serotonin syndrome (see section 2)
-
- allergic reactions, that may be serious, causing swelling of the face, lips, tongue or throat, difficulties breathing or swallowing, and/or a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- hives
- excessive or unexplained bleeding (including bruising, nose bleeding, gastrointestinal and vaginal bleeding
- rash

An increased risk of bone fractures has been observed in patients taking this type of medicines.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Brintellix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date that is stated on the packaging after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Brintellix contains

- The active substance is vortioxetine. Each film-coated tablet contains 5 mg vortioxetine (as hydrobromide).
- The other ingredients are mannitol (E421), microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate (type A), magnesium stearate, hypromellose, Macrogol 400, titanium dioxide (E171), iron oxide red (E172).

What Brintellix looks like and contents of the pack

Pink, almond-shaped 5 x 8.4 mm film-coated tablet (tablet) marked with “TL” on one side and “5” on the other side.

Brintellix film-coated tablets 5 mg are available in blister packs of 14, 28, 98, 56x1, 98x1, 126 (9x14) 490 (5x(98x1)) tablets and in tablet containers of 100 and 200 tablets.

The pack sizes of 56 x 1, 98 x 1 and 490 film-coated tablets are presented in unit dose blister.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

H. Lundbeck A/S
Ottiliavej 9
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY

Other sourses of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Brintellix 10 mg film-coated tablets
vortioxetine

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- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
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Warnings and precautions

Talk to your doctor or pharmacist before taking Brintellix if you:

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  - tramadol (a strong pain killer)
  - sumatriptan and similar medicines with active substance names ending in “triptans” (used to treat migraine).

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  Your doctor will treat you cautiously if you have a history of fits or have unstable fit disorder/epilepsy. Fits are a potential risk with medicines used to treat depression. Treatment should be discontinued in any patient who develops fits or where there is an increase in the frequency of fits.

- have had mania
- have a tendency to bleed or bruise easily.
- have low sodium level in the blood.
- are 65 years of age or older.
- have a severe kidney disease.
- have a severe liver disease or a liver disease called cirrhosis.

Thoughts of suicide and worsening of your depression

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

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Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

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Brintellix is not recommended in children and adolescents under 18 years due to lack of information for this age group.

Other medicines and Brintellix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:

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- moclobemide (a medicine to treat depression).
- selegiline, rasagiline (medicines to treat Parkinson's disease).
- linezolid (a medicine to treat bacterial infections).
- lithium (a medicine to treat depression and mental disorders) or tryptophan.
- medicines known to cause low sodium level.
- rifampicin (a medicine to treat tuberculosis and other infections)

- carbamazepine, phenytoin (medicines to treat epilepsy or other illness)
- Warfarin, dipyridamole, phenprocoumon, low-dose acetylsalicylic acid (blood thinning medicines).

Medicines that increase the risk of fits:
- sumatriptan and similar medicines with active substance names ending in “triptans”.
- tramadol (a strong painkiller).
- mefloquine (a medicine to prevent and treat malaria).
- bupropion (a medicine to treat depression also used to wean from smoking).
- fluoxetine, paroxetine and other medicines to treat depression called SSRI/SNRIs, tricyclics
- St John’s wort (hypericum perforatum)(a medicine to treat depression).
- quinidine (a medicine to treat heart rhythm disorders).
- chlorpromazine, chlorprothixene, haloperidol (medicines to treat mental disorders belonging to the group called phenothiazines, thioxanthenes, butyrophenones).

Please tell your doctor if you are taking any of the medicines above, since your doctor needs to know if you already are at risk for seizure.

Brintellix with alcohol

Combining this medicine with alcohol is not advisable.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

Brintellix should not be used during pregnancy unless the doctor says it is absolutely necessary.

If you take medicine to treat depression, including Brintellix, during the last 3 months of your pregnancy, you should be aware that the following effects may be seen in your newborn baby: trouble with breathing, bluish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. Contact your doctor immediately if your newborn baby has any of these symptoms.

Make sure your midwife and/or doctor know you are on Brintellix. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Brintellix may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.

Breast-feeding

It is expected that the ingredients of Brintellix will pass into breast milk. Brintellix is not to be used during breast-feeding. Your doctor will make a decision on whether you should stop breast-feeding, or stop using Brintellix taking into account the benefit of breast-feeding for your child, and the benefit of therapy for you

Driving and using machines

Brintellix has no or negligible influence on the ability to drive and use machines. However, as adverse reactions such as diziness have been reported, caution is advised during such activities when beginning Brintellix treatment or changing the dose.

3. How to take Brintellix

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Brintellix is 10 mg vortioxetine taken as one daily dose in adults less than 65 years of age. The dose may be increased by your doctor to a maximum of 20 mg vortioxetine per day or lowered to a minimum of 5 mg vortioxetine per day depending on your response to treatment.

For elderly people 65 years of age or older the starting dose is 5 mg vortioxetine taken once daily.

Method of administration

Take one tablet with a glass of water.
The tablet can be taken with or without food.

Duration of treatment

Take Brintellix for as long as your doctor recommends.

Continue to take Brintellix even if it takes some time before you feel any improvement in your condition.

Treatment should be continued for at least 6 months after you feel well again.

If you take more Brintellix than you should

If you take more than the prescribed dose of Brintellix, contact your doctor or nearest hospital emergency department immediately. Have the container and any remaining tablets available. Do this even if there are no signs of discomfort. Overdose signs could be dizziness, nausea, diarrhoea, stomach discomfort, itching of the whole body, sleepiness and flushing.

Following intake of dosages several times higher than the prescribed dose, fits (seizures) and a rare condition called serotonin syndrome have been reported.

If you forget to take Brintellix

Take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Brintellix

Do not stop taking Brintellix without talking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects were mild to moderate and occurred within the first two weeks of treatment. The reactions were usually temporary and did not lead to cessation of therapy.

Side effects listed below have been reported in the following frequencies.

Very common: may affect more than 1 in 10 people
- nausea

Common: may affect up to 1 in 10 people
- diarrhoea, constipation, vomiting
- dizziness
- itching of the whole body
- abnormal dreams

Uncommon: may affect up to 1 in 100 people
- flushing
- night sweats

Not known: frequency cannot be estimated from available data
- low levels of sodium in the blood (the symptoms may include feeling dizzy, weak, confused, sleepy or very tired, or feeling or being sick; more serious symptoms are fainting, fits or falls)
- serotonin syndrome (see section 2)
- allergic reactions, that may be serious, causing swelling of the face, lips, tongue or throat, difficulties breathing or swallowing, and/or a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- hives
- excessive or unexplained bleeding (including bruising, nose bleeding, gastrointestinal and vaginal bleeding
- rash

An increased risk of bone fractures has been observed in patients taking this type of medicines.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Brintellix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date that is stated on the packaging after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Brintellix contains

- The active substance is vortioxetine. Each film-coated tablet contains 10 mg vortioxetine (as hydrobromide).
- The other ingredients are mannitol (E421), microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate (type A), magnesium stearate, hypromellose, Macrogol 400, titanium dioxide (E171), iron oxide yellow (E172).

What Brintellix looks like and contents of the pack

Yellow, almond-shaped 5 x 8.4 mm film-coated tablet (tablet) marked with “TL” on one side and “10” on the other side.

Brintellix film-coated tablets 10 mg are available in blister packs of 7, 14, 28, 56, 56 x 1, 98, 98 x 1, 126 (9x14), 490 (5 x (98x1)) tablets and in tablet containers of 100 and 200 tablets.

The pack sizes of 56 x 1, 98 x 1 and 490 film-coated tablets are presented in unit dose blister.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

H. Lundbeck A/S
Ottiliavej 9
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sourses of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the patient

Brintellix 15 mg film-coated tablets
vortioxetine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Brintellix is and what it is used for
2. What you need to know before you take Brintellix
3. How to take Brintellix
4. Possible side effects
5. How to store Brintellix
6. Contents of the pack and other information

1. What Brintellix is and what it is used for

Brintellix contains the active substance vortioxetine.It belongs to a group of medicines called antidepressants.

Brintellix is used to treat major depressive episodes in adults.

Brintellix has been shown to reduce the broad range of depressive symptoms, including sadness, inner tension (feeling anxious), sleep disturbances (reduced sleep), reduced appetite, difficulty in concentrating, feelings of worthlessness, loss of interest in favourite activities, feeling of being slowed down.

2. What you need to know before you take Brintellix

Do not take Brintellix:

- if you are allergic to vortioxetine or any of the other ingredients of this medicine (listed in section 6).
- if you are taking other medicines for depression known as non-selective monoamine oxidase inhibitors or selective MAO-A inhibitors. Ask your doctor if you are uncertain.

Warnings and precautions

Talk to your doctor or pharmacist before taking Brintellix if you:

- are taking medicines with a so-called serotonergic effect, such as:
  - tramadol (a strong painkiller).
  - sumatriptan and similar medicines to Brintellix with active substance names ending in “triptans” (used to treatmigraine).