1. NAME OF THE MEDICINE

Brintellix 5 mg film-coated tablets,
Brintellix 10 mg film-coated tablets,
Brintellix 15 mg film-coated tablets,
Brintellix 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Brintellix 10 mg film-coated tablets
Each film-coated tablet contains vortioxetine hydrobromide equivalent to 10 mg of vortioxetine.

Brintellix 15 mg film-coated tablets
Each film-coated tablet contains vortioxetine hydrobromide equivalent to 15 mg of vortioxetine.

Brintellix 20 mg film-coated tablets
Each film-coated tablet contains vortioxetine hydrobromide equivalent to 20 mg of vortioxetine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Brintellix 5 mg film-coated tablets
Pink, almond-shaped film-coated tablet (5 x 8.4 mm), engraved with "TL" on one side and "5" on the other side.

Brintellix 10 mg film-coated tablets
Yellow, almond-shaped film-coated tablet (5 x 8.4 mm), engraved "TL" on one side and "10" on the other side.

Brintellix 15 mg film-coated tablets
Orange, almond-shaped film-coated tablet (5 x 8.4 mm), engraved "TL" on one side and "15" on the other side.

Brintellix 20 mg film-coated tablets
Red, almond-shaped film-coated tablet (5 x 8.4 mm), engraved with "TL" on one side and "20" on the other side.

4. CLINICAL DATA

4.1 Therapeutic indications

Brintellix is indicated for the treatment of major (i.e., characterized) depressive episodes in adults.

4.2 Dosage and method of administration

Dosage

The initial and recommended dosage of Brintellix is 10 mg of vortioxetine once daily in adults under 65 years of age.

Depending on the individual patient's response, the dose may be increased up to a maximum of 20 mg of vortioxetine once daily or decreased to a minimum of 5 mg of vortioxetine once daily.

After the disappearance of depressive symptoms, it is recommended to continue treatment for at least 6 months in order to consolidate the antidepressant response.

Stopping treatment

A gradual dose reduction may be considered to avoid discontinuation symptoms (see section 4.8). However, there are insufficient data to provide specific recommendations regarding a dose reduction schedule for patients treated with Brintellix.

Special populations

Elderly patients:
The lowest effective dose of 5 mg of vortioxetine once daily should always be used as the starting dose in patients aged 65 years and older. Caution is advised when treating patients aged 65 years and older with doses above 10 mg of vortioxetine once daily, as data are limited in this population (see section 4.4).

Cytochrome P450 inhibitors
Depending on the individual patient's response, administration of a lower dose of vortioxetine may be considered if a strong CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is combined with vortioxetine therapy (see section 4.5).

Cytochrome P450 inducers
Depending on the individual patient's response, dose adjustment of vortioxetine may be considered if a broad-spectrum cytochrome P450 inducer (e.g., rifampicin, carbamazepine, phenytoin) is combined with vortioxetine treatment (see section 4.5).

Pediatric population:
Brintellix should not be used in pediatric patients (under 18 years of age) with major depressive disorder (MDD) due to lack of demonstrated efficacy (see section 5.1). The safety of Brintellix in pediatric patients is described in sections 4.4, 4.8 and 5.1.

Renal or hepatic impairment
: No dose adjustment is necessary based on renal or hepatic function (see sections 4.4 and 5.2).

Method of administration

Brintellix should be administered orally.
The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Combination with non-selective monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Pediatric population

Brintellix should not be used in children and adolescents aged 7 to 17 years with TMD due to lack of demonstrated efficacy (see section 5.1). In general, the safety profile of vortioxetine in children and adolescents was comparable to that observed in adults, with the exception of a higher incidence of events associated with abdominal pain and a higher incidence of suicidal ideation, particularly in adolescents, compared to adults (see sections 4.8 and 5.1). Clinical studies in children and adolescents treated with antidepressants have shown a higher frequency of suicidal behavior (suicidal attempts and suicidal ideation) and hostile behavior (primarily aggression, oppositional behavior, anger) compared to 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. Because improvement may not appear during the first few weeks or more of treatment, patients should be closely monitored until such improvement is observed. General clinical experience suggests that the risk of suicide may increase during the early stages of recovery.

Patients with a history of suicidal behavior or those expressing significant suicidal ideation before starting treatment are at higher risk of experiencing suicidal thoughts or suicide attempts and should be closely monitored during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant use in adults with psychiatric disorders showed an increased risk of suicidal behavior in patients under 25 years of age treated with antidepressants compared to those receiving placebo.

Close monitoring of patients, particularly those at high risk, must accompany treatment, especially at the start of treatment and during dose changes. Patients (and their caregivers) should be advised of the need to monitor for clinical worsening, the emergence of suicidal behavior or thoughts, and any abnormal changes in behavior, and to seek immediate medical advice if these symptoms occur.

Convulsions

The occurrence of seizures is a potential risk associated with antidepressant treatment. Therefore, vortioxetine should be introduced with caution in patients with a history of seizures or patients with unstable epilepsy (see section 4.5). Treatment should be discontinued in any patient who develops seizures or in whom an increase in seizure frequency is observed.

Serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS)

Serotonin syndrome (SS) or neuroleptic malignant syndrome (NMS), which are life-threatening conditions, can occur with vortioxetine. The risk of SS or NMS is increased with concomitant use of serotonergic agents (including opiates and triptans), drugs that alter serotonin metabolism (including MAOIs), antipsychotics, and other dopamine antagonists. Patients should be monitored for signs and symptoms of SS or NMS (see sections 4.3 and 4.5).

Symptoms associated with serotonin syndrome include changes in mental status (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If these symptoms occur, vortioxetine treatment should be discontinued immediately and symptomatic treatment initiated.

Manic/hypomaniac episodes

Vortioxetine should be used with caution in patients with a history of manic/hypomanic episodes and should be discontinued in the event of a manic episode.

Aggression/agitation

Patients treated with antidepressants, including vortioxetine, may also experience feelings of anger, aggression, agitation, and irritability. The patient's health and disease status should be closely monitored. Patients (and their caregivers) should be advised to seek medical help if aggressive or agitated behavior occurs or worsens.

Hemorrhage

Bleeding abnormalities, such as bruising, purpura, and other bleeding disorders, including gastrointestinal or gynecological bleeding, have been rarely reported with antidepressants that have a serotonergic effect, including vortioxetine. SSRIs and SNRIs may increase the risk of postpartum hemorrhage, and this risk may also apply to vortioxetine (see section 4.6). Caution is advised in patients taking anticoagulants and/or drugs known to impair 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.

Hyponatremia

Hyponatremia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported in rare cases with the use of antidepressants that have a serotonergic effect (SSRIs, SNRIs). Caution should be exercised in at-risk patients, such as the elderly, patients with liver cirrhosis, or when used concomitantly with drugs known to cause hyponatremia.
Discontinuation of vortioxetine should be considered in patients with symptomatic hyponatremia, and appropriate medical management should be initiated.

Glaucoma

Cases of mydriasis associated with the use of antidepressants, including vortioxetine, have been reported. This mydriatic effect can cause narrowing of the iridocorneal angle, resulting in increased intraocular pressure and the development of angle-closure glaucoma. Caution is advised when prescribing vortioxetine to patients with elevated intraocular pressure or at risk of acute angle-closure glaucoma.

Elderly people

Data on the use of Brintellix in elderly patients with major depressive episodes are limited. Therefore, caution should be exercised when treating patients aged 65 years and over with doses exceeding 10 mg of vortioxetine once daily (see sections 4.2, 4.8 and 5.2).

Kidney or liver failure

Given the vulnerability of patients with renal or hepatic impairment and the limited data on the use of Brintellix in these subpopulations, caution should be exercised when treating these patients (see sections 4.2 and 5.2).

Brintellix contains sodium

This medicine contains less than 1 mmol of sodium (23 mg) per tablet, that is to say it is essentially 'sodium free'.

4.5 Interactions with other medicinal products and other forms of interaction

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

Effects of other medications on vortioxetine

Irreversible non-selective MAOIs:
Due to the risk of serotonin syndrome, vortioxetine is contraindicated in combination with irreversible non-selective MAOIs. Vortioxetine treatment should not be initiated for at least 14 days after discontinuation of an irreversible non-selective MAOI. Vortioxetine should be discontinued 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 is necessary, the added drug should be administered at the lowest dose, and under close clinical monitoring for the development of serotonin syndrome (see section 4.4).

Non-selective reversible MAOI (linezolid):
The combination of vortioxetine with a reversible, non-selective MAOI, such as the antibiotic linezolid, is contraindicated (see section 4.3). If the combination is necessary, the added drug should be administered at the lowest dose, and under close clinical monitoring for the development of serotonin syndrome (see section 4.4).

Selective Irreversible MAO-B Inhibitors (selegiline, rasagiline):
Although the risk of serotonin syndrome is lower with selective MAO-B inhibitors than with MAO-A inhibitors, caution should be exercised when vortioxetine is used in combination with irreversible MAO-B inhibitors such as selegiline or rasagiline. In such cases, the development of serotonin syndrome should be closely monitored (see section 4.4).

Serotonergic drugs
The combination of drugs having a serotonergic effect, for example opiates (in particular tramadol) and triptans (in particular sumatriptan) may lead to serotonin syndrome (see section 4.4).

St. John's wort:
The simultaneous use of serotonergic antidepressants and herbal preparations containing St. John's wort (*Hypericum perforatum*) may increase the incidence of adverse effects, including serotonin syndrome (see section 4.4).
Drugs that lower the seizure threshold:
Serotonergic antidepressants may lower the seizure threshold. Caution is advised when used in combination with other drugs that may lower the seizure threshold [e.g., antidepressants (tricyclics, SSRIs, SNRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion, tramadol] (see section 4.4).

ECT (electroconvulsive therapy)
Due to the lack of clinical experience with the administration of vortioxetine concurrently with ECT, caution is advised.

CYP2D6 Inhibitors:
When vortioxetine 10 mg/day was co-administered with bupropion (a potent CYP2D6 inhibitor) 150 mg twice daily for 14 days in healthy subjects, the Area Under the Curve (AUC) was increased 2.3-fold. Co-administration resulted in a higher incidence of adverse events when bupropion was added to vortioxetine compared to when vortioxetine was added to bupropion. Depending on the individual patient's response, a lower dose of vortioxetine may be considered when a potent CYP2D6 inhibitor (e.g., bupropion, quinidine, fluoxetine, paroxetine) is co-administered with vortioxetine (see section 4.2).

CYP3A4 inhibitors and CYP2C9 and CYP2C19 inhibitors
: When vortioxetine was co-administered after 6 days of treatment with ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) or after 6 days of treatment with fluconazole 200 mg/day (a CYP2C9, CYP2C19, and CYP3A4/5 inhibitor) in healthy subjects, the AUC of vortioxetine was increased by a factor of 1.3 and 1.5, respectively. No dose adjustment is necessary.

No inhibitory effect of a single 40 mg dose of omeprazole (CYP2C19 inhibitor) on the multiple-dose pharmacokinetics of vortioxetine was observed in healthy subjects.

Interactions in CYP2D6 Poor Metabolizers:
The administration of strong CYP3A4 inhibitors (such as itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, conivaptan and many HIV protease inhibitors) and CYP2C9 inhibitors (such as fluconazole and amiodarone) in CYP2D6 poor metabolizers (see section 5.2) has not been specifically studied, but it is anticipated that it will lead to a greater increase in vortioxetine exposure in these patients, compared to the moderate effects described above. Depending on the individual patient's response, administration of a lower dose of vortioxetine may be considered if a strong inhibitor of CYP3A4 or CYP2C9 is co-administered in poor metabolizers of CYP2D6.

Cytochrome P450 Inducers:
When a single 20 mg dose of vortioxetine was co-administered after 10 days of rifampicin 600 mg/day (a broad-spectrum inducer of CYP isoenzymes) in healthy subjects, a 72% decrease in the AUC of vortioxetine was observed. Depending on the individual patient's response, dose adjustment may be considered if a broad-spectrum cytochrome P450 inducer (e.g., rifampicin, carbamazepine, phenytoin) is used concomitantly with vortioxetine (see section 4.2).

Alcohol:
When a single dose of 20 mg or 40 mg vortioxetine was co-administered with a single dose of ethanol (0.6 g/kg) in healthy subjects, no effect on the

pharmacokinetics of either vortioxetine or ethanol was observed, and no significant impairment of cognitive function was observed compared to placebo. However, alcohol consumption is not recommended during antidepressant treatment.

Acetylsalicylic acid:
No effect was observed on the pharmacokinetics of vortioxetine when multiple doses of acetylsalicylic acid 150 mg/day were observed in healthy subjects.

Effects of vortioxetine on other drugs

Anticoagulant and antiplatelet drugs:
No significant effects compared to placebo were observed on INR, prothrombin time, or plasma R-/S-warfarin values following multiple-dose co-administration of vortioxetine with stable doses of warfarin in healthy subjects. Similarly, no significant inhibitory effect compared to placebo was observed on platelet aggregation or the pharmacokinetics of acetylsalicylic acid or salicylic acid when acetylsalicylic acid 150 mg/day was co-administered following multiple doses of vortioxetine in healthy subjects. However, caution should be exercised when vortioxetine is combined with oral anticoagulant or antiplatelet drugs or with drugs used to relieve pain (e.g., acetylsalicylic acid or NSAIDs) because of a potential increase in the risk of bleeding due to a pharmacodynamic interaction (see section 4.4).

Cytochrome P450 substrates
In vitro, vortioxetine did not show any significant potential for inhibition or induction of cytochrome P450 isoenzymes (see section 5.2).

After multiple doses of vortioxetine, no inhibitory effect was observed in healthy subjects of the cytochrome P450 isoenzymes CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinyl estradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or CYP2D6 (dextromethorphan).

No pharmacodynamic interactions or significant impairment of cognitive function were observed compared to placebo with vortioxetine after co-administration of a single 10 mg dose of diazepam. No significant effects on sex hormone levels were observed compared to placebo after co-administration of vortioxetine with a combined oral contraceptive (30 µg ethinyl estradiol/150 µg levonorgestrel).

Lithium, tryptophan:
No clinically significant effects were observed following steady-state lithium exposure after co-administration with multiple doses of vortioxetine in healthy subjects. However, potentiation of effects has been reported when serotonergic antidepressants were administered concomitantly with lithium or tryptophan; therefore, caution should be exercised when vortioxetine is used concurrently with these drugs.

Interference with urine drug screening:
False positives have been reported in urine enzyme immunoassay tests for methadone in patients receiving vortioxetine. Caution should be exercised when interpreting a positive urine drug screening result; confirmation by another analytical method (e.g., chromatography) should be considered.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Data on the use of vortioxetine in pregnant women are limited.
Animal studies have shown reproductive toxicity (see section 5.3).

The following symptoms may occur in the newborn after maternal use of a serotonergic drug late in pregnancy: respiratory distress, cyanosis, apnea, seizures, unstable temperature, feeding difficulties, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremors, tremors, irritability, lethargy, persistent crying, drowsiness, and sleep disturbances. These symptoms could be due to discontinuation of the medication or to excessive serotonergic activity. In most cases, these complications began immediately or very soon after birth (<24 hours).

Epidemiological data suggest that the use of SSRIs during pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Although the association between PPHN and vortioxetine treatment has not been studied, this potential risk cannot be ruled out given the associated mechanism of action (increased serotonin concentrations).

Brintellix should only be administered to pregnant women if the expected benefits outweigh the potential risks to the fetus.

Data from observational studies have shown an increased risk (less than 2-fold) of postpartum hemorrhage following exposure to SSRIs or SNRIs in the month preceding birth. Although no studies have analyzed the association between vortioxetine treatment and postpartum hemorrhage, a potential risk exists, given the associated mechanism of action (see section 4.4).

Breastfeeding

Limited published data show that vortioxetine is excreted in small amounts in breast milk, with an estimated relative infant dose (RID *)* of less than 2%. No adverse drug-related effects have been observed in infants.

However, the available clinical data are limited and a risk to the breastfed infant cannot be excluded.

The decision must be made to stop breastfeeding or to stop/interrupt treatment with Brintellix taking into account the benefits of breastfeeding for the child and the benefits of treatment for the woman.

Fertility

Fertility studies conducted in male and female rats showed no effect of vortioxetine on fertility, sperm quality, or mating ability (see section 5.3). Reported cases in humans with drugs from the SSRI class have shown an effect on sperm quality, which is reversible. No effects on human fertility have been observed to date.

4.7 Effects on the ability to drive vehicles and use machinery

Brintellix has no or negligible influence on the ability to drive and use machines. However, as side effects such as dizziness have been reported, patients should exercise caution when driving or operating dangerous machinery, particularly when starting vortioxetine treatment or when changing the dose.

4.8 Side effects

Security Profile Summary

The most frequent side effect was nausea.

Tabulated list of side effects

Adverse reactions are summarized 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 or post-marketing experience.

ORGAN SYSTEM CLASS	FREQUENCY	SIDE EFFECT
Immune system disorders	Frequency not known*	Anaphylactic reaction
Endocrine disorders	Frequency not known*	Hyperprolactinemia, in some cases associated with galactorrhea
Metabolism and nutrition disorders	Frequency not known*	Hyponatremia
Psychiatric disorders	Frequent	Abnormal dreams
	Uncommon	Hallucinations
	Frequency not known*	Insomnia , agitation, aggression (see section 4.4)
Disorders of the nervous system	Frequent	Dizzying sensations
	Uncommon	Tremors
	Frequency not known*	Serotonin syndrome, Headaches, Akathisia, Bruxism, Trismus , Restless legs syndrome
Eye conditions	Uncommon	Blurred vision
	Rare	Mydriasis (which can lead to acute angle-closure glaucoma, see section 4.4)
Vascular disorders	Uncommon	Hot flashes
	Frequency not known*	Hemorrhage (including contusions, bruises, nosebleeds, gastrointestinal or vaginal bleeding)
Gastrointestinal disorders	Very common	Nausea
	Frequent	Diarrhea, Constipation, Vomiting, Dyspepsia
Skin and subcutaneous tissue disorders	Frequent	Pruritus, including generalized pruritus ; Hyperhidrosis
	Uncommon	Night sweats
	Frequency not known*	Angioedema, Urticaria, Rash
General disorders and administration site abnormalities	Frequency not known*	Treatment discontinuation syndrome

* Based on post-marketing cases

Description of a selection of side effects

Nausea
was generally mild to moderate and occurred within the first two weeks of treatment. The effects were usually transient and, in most cases, did not require discontinuation of treatment. Gastrointestinal side effects, such as nausea, occurred more frequently in women than in men.

Elderly patients
: For doses of vortioxetine 10 mg once daily or higher, the trial discontinuation rate was higher in patients aged 65 years and older.
For doses of vortioxetine 20 mg once daily, the incidence of nausea and constipation was higher in patients aged 65 years and older (42% and 15%, respectively) than in patients under 65 years of age (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 compared to placebo. However, the 20 mg dose of vortioxetine was associated with an increase in treatment-emergent sexual dysfunction (TESD) (see section 5.1). Cases of sexual dysfunction have been reported post-marketing with vortioxetine doses lower than 20 mg.

Class effect:
Epidemiological studies, primarily conducted in patients aged 50 and over, show an increased risk of bone fractures in patients receiving medication from the SSRI or tricyclic antidepressant classes. The mechanism explaining this risk is unknown, and it is unclear whether vortioxetine is involved in this risk.

Pediatric population
: A total of 304 children aged 7 to 11 years and 308 adolescents aged 12 to 17 years with major depressive disorder (MDD) were treated with vortioxetine in two double-blind, placebo-controlled studies , respectively. Overall, the safety profile of vortioxetine in children and adolescents was comparable to that observed in adults, with the exception of a higher incidence of events associated with abdominal pain and a higher incidence of suicidal ideation, particularly in adolescents, compared to adults (see section 5.1).

Two open-label, long-term extension studies were conducted with vortioxetine doses of 5 to 20 mg/day, for treatment durations of 6 months (N=662) and 18 months (N=94), respectively. Overall, the safety and tolerability profile of vortioxetine in the pediatric population after long-term use was comparable to that observed after short-term use.

Symptoms related to discontinuation of vortioxetine treatment:
In clinical studies, symptoms related to discontinuation of treatment were systematically assessed following abrupt discontinuation of vortioxetine. No clinically relevant differences were observed compared to placebo in terms of the incidence or nature of symptoms related to discontinuation of vortioxetine treatment (see section 5.1). Post-marketing reports of cases describing symptoms related to discontinuation of treatment have been received, and these symptoms included, but were not limited to, dizziness, headache, sensory disturbances (including paresthesia, electric shock sensations), sleep disturbances (including insomnia), nausea and/or vomiting, anxiety, irritability, agitation, fatigue, and tremors. These symptoms may occur during the first week following discontinuation of vortioxetine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals report any suspected adverse reactions via

Belgium
Federal Agency for Medicines and Health Products
www.afmps.be
Vigilance Division:
Website: www.notifieruneffetindesirable.be
e-mail: adr@fagg-afmps.be

Luxembourg
Regional Pharmacovigilance Centre in Nancy or Pharmacy and Medicines Division of the Directorate of Health
Website: www.guichet.lu/pharmacovigilance

4.9 Overdose

Ingestion of vortioxetine during clinical trials in the dosage range of 40 mg to 75 mg caused an aggravation of the following adverse effects: nausea, postural dizziness, diarrhea, abdominal discomfort, generalized pruritus, drowsiness and hot flashes.

Post-marketing experience mainly concerns overdoses of vortioxetine 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.

Data on vortioxetine overdoses above 80 mg are limited. Cases of seizures and serotonin syndrome have been reported at doses several times higher than the therapeutic range.

Management of overdoses consists of treating clinical symptoms and providing appropriate monitoring. Medical follow-up in a specialized setting is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Psychoanaleptics, Other antidepressants, ATC code: N06AX26

Mechanism of action

The mechanism of action of vortioxetine is thought to be related to the direct modulation of serotonergic receptor activity and the inhibition of the serotonin (5-HT) transporter. Non-clinical data indicate that vortioxetine is an antagonist of 5-HT3 , 5- $_{HT7}$, and 5-HT1D $_{receptors}$, a partial agonist of 5-HT1B receptors $_{, an\ agonist\ of\ 5-\ HT1A}$ receptors , and an inhibitor of the 5-HT transporter, leading to the modulation of neurotransmission in several systems. These systems primarily affect serotonin, but likely also norepinephrine, dopamine, histamine, acetylcholine, GABA, and glutamate. This multimodal activity is considered responsible for the antidepressant and anxiolytic effects, as well as the improvements in cognitive function, learning, and memory observed with vortioxetine in animals. However, the precise contribution of individual targets to the observed pharmacodynamic profile is still poorly understood, and caution is advised when extrapolating animal data directly to humans.

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

Clinical efficacy and safety

The efficacy and safety of vortioxetine were studied in a clinical program involving over 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, fixed-dose studies of 6 to 8 weeks were conducted to explore the short-term efficacy of vortioxetine in adult (including elderly) MDD. The efficacy of vortioxetine was demonstrated for at least one dose in 9 of the 12 studies, with at least a 2-point difference in the total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D- $_{24}$) *versus* placebo. Its clinical relevance was confirmed, demonstrated by the proportions of responding patients and those experiencing remission, as well as by the improvement in the CGI-I (Clinical Global Impression – Global Improvement) score. The efficacy of vortioxetine increased with the dose.

The effect across different studies was confirmed by a meta-analysis (MMRM) examining the mean change from baseline in the total MADRS score at week 6/8 in short-term, placebo-controlled studies. In this meta-analysis, the difference *versus placebo across 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 dosages ,* respectively. The results at the 15 mg/day dosage were not different from placebo in the meta-analysis, but the mean difference was -2.6 points. The efficacy of vortioxetine is confirmed by the pooled analysis of responders, in which the proportion of responders was 46% to 49% for vortioxetine *versus* 34% for placebo (p<0.01, NRI analysis).

In addition, vortioxetine, in the dosage range of 5 to 20 mg/day, has shown efficacy on a wide range of depressive symptoms (assessed by improvement in all scores of the MADRS scale items taken one by one).

The efficacy of vortioxetine 10 or 20 mg/day was more broadly demonstrated in a 12-week, double-blind, variable-dose comparative study *versus* agomelatine 25 or 50 mg/day in patients with TMD. Vortioxetine was statistically significantly superior to agomelatine as measured by the improvement in the total MADRS score, and these results were confirmed by the clinical relevance demonstrated by the proportion of responding patients and patients achieving remission, as well as by the improvement in the CGI-I score.

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 randomized to receive vortioxetine at a dose of 5 or 10 mg/day or placebo, and the occurrence of relapse was monitored for a double-blind period of at least 24 weeks (range 24 to 64 weeks). Vortioxetine was superior (p = 0.004) to placebo on the primary endpoint, time to relapse of depressive disorder, with a relative risk of 2.0; in other words, the risk of relapse was twice as high in the placebo group as in the vortioxetine group.

Elderly patients
In the 8-week, fixed-dose, double-blind, placebo-controlled study conducted in depressed patients (aged 65 years and over, n=452, including 156 on vortioxetine), vortioxetine 5 mg/day was superior to placebo in improving total MADRS and HAM-D scores . A difference of $_{4.7}$ points in the total MADRS score was observed with vortioxetine *versus* placebo at week 8 (MMRM analysis).

Patients with severe depression or depression and high levels of anxiety symptoms:
In patients with severe depression (baseline MADRS total score ≥30) and in depressed patients with high levels of anxiety symptoms (baseline HAM-A total score ≥20), vortioxetine has also demonstrated efficacy in short-term studies in adults (the mean difference in total MADRS score at week 6/8 *versus* placebo was 2.8 to 7.3 points and 3.6 to 7.3 points, respectively (MMRM analysis)). In the study conducted in the elderly population, vortioxetine was also effective in these patients.
Maintenance of antidepressant efficacy was also demonstrated in this patient population in the long-term relapse prevention study.

Effects of vortioxetine on scores of the Digit Symbol Substitution Test (DSST), the University of California San Diego Performance-Based Skills Assessment (UPSA) (objective measures), the Perceived Deficits Questionnaire (PDQ), and the Cognitive and Physical Functioning Questionnaire (CPFQ) (subjective measures).
The efficacy of vortioxetine (5–20 mg/day) in patients with TMD was studied in three short-term, placebo - controlled studies (two in adults and one in elderly patients).

Vortioxetine had a statistically significant effect *versus* placebo on the Digit Symbol Substitution Test (DSST), with a difference ranging from 1.75 (p=0.019) to 4.26 (p<0.0001) in the two adult studies and a difference of 2.79 (p=0.023) in the elderly patient study. In meta-analyses (ANCOVA, LOCF) of these three studies examining the mean change in the number of correct symbols for the DSST from baseline, the effect size for the difference between vortioxetine and placebo was 0.35 (p<0.05). Adjusting the analysis for the change in MADRS scores, the meta-analysis of the same studies showed a difference in the total score between vortioxetine and placebo (p<0.05) with an effect size of 0.24.

A study analyzed the effect of vortioxetine on functional capacity using the UPSA (University of California San Diego Performance-Based Skills Assessment) test. The results for vortioxetine were statistically different from those of the placebo: 8.0 points for vortioxetine and 5.1 points for the placebo (p=0.0003).

In one study, vortioxetine was superior to placebo on subjective measures assessed by the Perceived Deficits Questionnaire. The scores were -14.6 for vortioxetine and -10.5 for placebo (p=0.002). Vortioxetine's results were not different from placebo's on subjective measures assessed using the Cognitive and Physical Functioning Questionnaire. The scores were -8.1 for vortioxetine and -6.9 for placebo (p=0.086).

Safety and Tolerability:
The safety and tolerability of vortioxetine have been established in short- and long-term studies with dosage ranges from 5 to 20 mg/day. For further information on adverse effects, see section 4.8.
Vortioxetine did not increase the incidence of insomnia or somnolence compared to placebo.

In short- and long-term placebo-controlled clinical trials, the risk of potential withdrawal symptoms was systematically assessed after abrupt discontinuation of vortioxetine. No clinically relevant differences were observed compared to placebo in the incidence or nature of withdrawal symptoms after short-term (6 to 12 weeks) or long-term (24 to 64 weeks) vortioxetine treatment.

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

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

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

No clinically significant changes in liver or kidney function were observed in clinical studies.

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

Pediatric population: Two short-term, randomized, double-blind, placebo -
controlled studies with an active comparator (fluoxetine) and fixed doses (vortioxetine 10 mg/day and 20 mg/day) were conducted; one in children aged 7 to 11 years with TMD, and the other in adolescents aged 12 to 17 years with TMD. These studies included a 4-week pre-randomization period with single-blind placebo administration combined with standardized psychosocial intervention (patients treated in the pediatric study: N=677; in the adolescent study: N=777); only patients who did not respond during the pre-randomization period were randomized (child study: N=540; adolescent study: N=616).

In the study of children aged 7 to 11 years, the mean effect of the two vortioxetine doses of 10 and 20 mg/day was not statistically significantly different from the effect of placebo, based on the total score of the Child Depression Rating Scale-Revised (CDRS-R) at week 8. The active comparator (fluoxetine 20 mg/day) and the individual doses of vortioxetine (10 and 20 mg/day) also showed no nominally significant difference compared to placebo. Overall, the safety profile of vortioxetine in children was comparable to that observed in adults, with the exception of abdominal pain, which occurred at a higher incidence in children. The treatment discontinuation rate due to adverse events was 2.0% in patients treated with vortioxetine 20 mg/day, 1.3% in patients treated with vortioxetine 10 mg/day, and 0.7% in patients treated with placebo; there were no treatment discontinuations in patients treated with fluoxetine. The most frequently reported adverse events in the vortioxetine groups were nausea, headache, vomiting, dizziness, and abdominal pain. The incidence of nausea, vomiting, and abdominal pain was higher in the vortioxetine groups than in the placebo group. Suicidal ideation and behavior were reported during the 4-week single-blind pre-randomization period (placebo 2/677 [0.3%]) and during the 8-week treatment period (vortioxetine 10 mg/day 1/149 [0.7%], placebo 1/153 [0.7%]). In addition, the event "active nonspecific suicidal ideation" was reported on the C-SSRS scale in 5 patients during the 8-week treatment period (vortioxetine 20 mg/day 1/153 [0.7%], placebo 1/153 [0.7%], and fluoxetine 3/82 [3.7%]). Suicidal ideation and behavior, assessed using the Columbia Suicide Risk Severity Rating Scale (C-SSRS), were comparable between treatment groups.

In the study of adolescents aged 12 to 17 years, the total score on the Child Depression Rating Scale-Revised (CDRS-R) did not demonstrate a statistically significant superiority of either dose of vortioxetine (10 mg/day and 20 mg/day) over placebo. The total CDRS-R score obtained with the active comparator (fluoxetine 20 mg/day) was statistically different from that obtained with placebo. Overall, the safety profile of vortioxetine in adolescents was comparable to that observed in adults, with the exception of abdominal pain and suicidal ideation, which were observed at higher incidences in adolescents compared to adults. The rate of treatment discontinuation due to adverse events (primarily suicidal ideation and nausea and vomiting) was higher in patients treated with vortioxetine 20 mg/day (5.6%) than in patients treated with vortioxetine 10 mg/day (2.7%), fluoxetine (3.3%), or placebo (1.3%). The most frequently reported adverse events in the vortioxetine treatment groups were nausea, vomiting, and headache. Adverse events such as suicidal ideation and behavior were reported during the 4-week single-blind pre-randomization period (placebo 13/777 [1.7%]) and during the 8-week treatment period (vortioxetine 10 mg/day 2/147 [1.4%], vortioxetine 20 mg/day 6/161 [3.7%], fluoxetine 6/153 [3.9%], placebo 0/154 [0%]). Suicidal ideation and behavior, assessed using the C-SSRS scale, were comparable between the treatment groups.

Brintellix should not be used in pediatric patients (aged less than 18 years) suffering from major depressive disorder (see section 4.2).

The European Medicines Agency has granted a waiver from the obligation to submit the results of studies carried out in major depressive disorder with vortioxetine in children under 7 years of age (information on pediatric use: see section 4.2).

5.2 Pharmacokinetic properties

Absorption:
Vortioxetine is slowly but well absorbed after oral administration, with peak plasma concentrations reached within 7 to 11 hours. Following multiple daily doses of 5, 10, or 20 mg, mean Cmax values $_{ranging}$ from 9 to 33 ng/mL were observed. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics of vortioxetine has been observed (see section 4.2).

Distribution:
The mean volume of distribution (Vss $_{)}$ is 2600 L, indicating extensive extravascular distribution. Vortioxetine is highly bound to plasma proteins (98–99%), and binding appears to be independent of plasma vortioxetine concentrations.

Biotransformation
Vortioxetine is extensively metabolized in the liver, primarily by oxidation by CYP2D6 and to a lesser extent by CYP3A4/5 and CYP2C9, followed by conjugation with glucuronic acid.

No inhibitory or inducing effects of vortioxetine were observed in drug interaction studies for the isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 (see section 4.5). Vortioxetine is a weak substrate and inhibitor of P-gp.

The main metabolite of vortioxetine is pharmacologically inactive.

Elimination:
The mean elimination half-life and oral clearance are 66 hours and 33 L/h, respectively. Approximately two-thirds of the inactive metabolites of vortioxetine are excreted in the urine and approximately one-third in the feces. Only negligible amounts of vortioxetine are excreted in the feces. Steady-state plasma concentrations are reached in approximately two weeks.
Linearity/Non-linearity:
Pharmacokinetics are linear and time-independent within the studied dosage range (2.5 to 60 mg/day).

In accordance with the half-life, the accumulation index is between 5 and 6 based on the AUC $_{0\text{-}24h}$ after administration of multiple doses of 5 to 20 mg/day.

Special populations
Elderly
In healthy elderly subjects (aged ≥65 years; n = 20), vortioxetine exposure increased by 27% (Cmax $_{and}$ AUC) compared to healthy young control subjects (aged ≤45 years) after multiple doses of 10 mg/day. The lowest effective dose of 5 mg of vortioxetine once daily should always be used to initiate treatment in patients aged 65 years and older (see section 4.2). However, caution should be exercised when prescribing to elderly patients at doses above 10 mg of vortioxetine once daily (see section 4.4).

Renal impairment:
Following a single 10 mg dose of vortioxetine, renal impairment, as defined by the Cockcroft-Gault formula (mild, moderate, or severe; n = 8 per group), resulted in modest increases in exposure (up to 30%) compared to matched healthy controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during dialysis (AUC and Cmax $_{were}$ 13% and 27% lower, respectively; n = 8) after a single 10 mg dose of vortioxetine. No dose adjustment is necessary based on renal function (see sections 4.2 and 4.4).

Hepatic Impairment:
The pharmacokinetic parameters of patients (N=6 to 8) with mild, moderate, or severe hepatic impairment (Child-Pugh criteria A, B, or C, respectively) were compared to those of healthy volunteers. AUC was lower, with changes of less than 10% in patients with mild or moderate hepatic impairment and greater than 10% in patients with severe hepatic impairment. The change in Cmax $_{was}$ less than 25% lower in all groups. No dose adjustment is necessary based on hepatic function (see sections 4.2 and 4.4).

CYP2D6 Genetic Polymorphism:
Plasma concentrations of vortioxetine were approximately twice as high in CYP2D6 poor metabolizers compared to extensive metabolizers. Administration of strong CYP3A4/2C9 inhibitors to CYP2D6 poor metabolizers could potentially result in greater drug exposure (see section 4.5).

In CYP2D6 ultra-rapid metabolizers, the plasma concentration of vortioxetine 10 mg/day was comparable to that obtained in rapid metabolizers at doses between 5 mg/day and 10 mg/day.
Dose adjustment may be considered depending on individual response (see section 4.2).

Pediatric population:
The pharmacokinetic parameters of vortioxetine following administration of 5 to 20 mg orally once daily were characterized in a pediatric population with major depressive disorder using population-based modeling techniques based on data from one pharmacokinetic study (7-17 years) and two efficacy and safety studies (7-17 years). The pharmacokinetic parameters of vortioxetine in the pediatric population were comparable to those observed in adult patients.

5.3 Preclinical safety data

Administration of vortioxetine in general toxicity studies in mice, rats, and dogs was primarily associated with clinical signs affecting the central nervous system. These included salivation (rats and dogs), pupil dilation (dogs), and two episodes of seizures in dogs. Regarding seizures, a no-observed-adverse-effect level (NOAEL) was established with a safety margin of 5, based on the maximum recommended therapeutic dose of 20 mg/day. In terms of toxicity, target organs were limited to the kidneys (rats) and the liver (mice and rats). Kidney changes in rats (glomerulonephritis, renal tubule obstruction, crystalline substances in the renal tubules) and liver changes in mice and rats (hepatocellular hypertrophy, hepatocyte necrosis, bile duct hyperplasia, crystalline substances in the bile ducts) were observed at exposures more than 10 times (mice) and 2 times (rats) higher than human exposure at the maximum recommended therapeutic dose of 20 mg/day. These findings were attributed primarily to obstruction of the renal tubules and bile ducts by rodent-specific crystalline substances bound to vortioxetine; this is considered a low risk for humans.

Vortioxetine did not show genotoxic potential in a standard battery of *in vitro* and *in vivo* tests .

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

Vortioxetine had no effect on fertility, mating ability, reproductive organs, or sperm morphology and motility in rats. Vortioxetine had no teratogenic effects in rats or rabbits. Reproductive toxicity, in terms of effects on fetal weight and delayed ossification, was observed in rats at exposures more than 10 times higher than human exposure at the maximum recommended therapeutic dose of 20 mg/day. Similar effects were observed in rabbits at subtherapeutic exposures.

In a pre- and postnatal study in rats, vortioxetine was associated with increased neonatal mortality, reduced weight gain and delayed development of neonatal infants, at doses that did not lead to maternal toxicity and with exposures similar to those achieved in humans after administration of vortioxetine at a dose of 20 mg/day (see section 4.6).

Substances related to vortioxetine were distributed in the milk of lactating rats (see section 4.6).

In juvenile toxicity studies in rats, all results related to vortioxetine treatment were consistent with those observed in adult animals.

Environmental risk assessment studies have shown that vortioxetine can potentially be persistent, bioaccumulative, and toxic to the environment (harmful to fish). Nevertheless, the risk of using vortioxetine under the recommended conditions is considered negligible for the aquatic and terrestrial environment (see section 6.6).

6. PHARMACEUTICAL DATA

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),
Red iron oxide (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),
Yellow iron oxide (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),
Red iron oxide (E172),
Yellow iron oxide (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)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicine does not require any special storage precautions.

6.5 Nature and contents of the outer packaging

Brintellix 5 mg film-coated tablets.
Blister pack: Transparent; PVC/PVdC/aluminium.
Pack sizes: 14, 28 and 98 film-coated tablets.

Perforated unit-dose blister packs: PVC/PVdC/aluminium.
Presentations: 56x1 and 98x1 film-coated tablets.
Multipacks containing 126 (9x14) and 490 (5 x (98x1)) film-coated tablets.

High-density polyethylene (HDPE) bottle.
Presentations: 100 and 200 film-coated tablets.

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

Perforated unit-dose blister packs: PVC/PVdC/aluminium.
Presentations: 56 x 1 and 98 x 1 film-coated tablets.
Multipacks containing 126 (9 x 14) and 490 (5 x (98 x 1)) film-coated tablets.

High-density polyethylene (HDPE) bottle.
Presentations: 100 and 200 film-coated tablets.

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

Perforated unit-dose blister packs: PVC/PVdC/aluminum.
Presentations: 56 x 1 and 98 x 1 film-coated tablets.
Multipack containing 490 (5 x (98 x 1)) film-coated tablets.

High-density polyethylene (HDPE) bottle.
Pack sizes: 100 and 200 film-coated tablets.
Brintellix 20 mg film-coated tablets.
Blister pack: Transparent; PVC/PVdC/aluminum.
Pack sizes: 14, 28, 56, and 98 film-coated tablets.

Perforated unit-dose blister packs: PVC/PVdC/aluminium.
Presentations: 56 x 1 and 98 x 1 film-coated tablets.
Multipacks containing 126 (9 x 14) and 490 (5 x (98 x 1)) film-coated tablets.

High-density polyethylene (HDPE) bottle.
Pack sizes: 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 regulations.

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 AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of initial authorization: December 18, 2013.
Date of last renewal: November 20, 2018.

10. TEXT UPDATE DATE

11/2025

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