PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTRINTELLIX®

Vortioxetine (as vortioxetine hydrobromide)

5 mg, 10 mg, 15 mg, and 20 mg tablets, Oral

Antidepressant

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Date of Initial Approval:
Oct. 22, 2014

Date of Revision:
March 11, 2021

Submission Control No: 237793

RECENT MAJOR LABEL CHANGES

Not Applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRINTELLIX (vortioxetine hydrobromide tablet) is indicated for:

- the treatment of major depressive disorder (MDD) in adults.

The efficacy of TRINTELLIX in providing symptomatic relief of MDD was demonstrated in double-blind, placebo-controlled clinical trials of up to 8 weeks duration (see CLINICAL TRIALS, Study Results).

The efficacy of TRINTELLIX in maintaining an antidepressant response for up to 24 weeks was demonstrated in a double-blind, placebo-controlled trial in patients with MDD who initially responded to 12-weeks of acute, open label treatment with TRINTELLIX (see CLINICAL TRIALS, Study Results).

Physicians who elect to use TRINTELLIX for extended periods should periodically re-evaluate the usefulness of the drug for individual patients.

1.1 Pediatrics

Pediatrics (<18 years of age):Based on the data submitted and reviewed by Health Canada, the efficacy of Trintellix in adolescents aged 12 to 17 years have not been demonstrated. The safety and efficacy in children aged 7 to 11 years has not yet been established. Therefore, TRINTELLIX is not indicated for use in patients below the age of 18 (see WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM; (see WARNINGS AND PRECAUTIONS**,** Potential Association With Behavioural And Emotional Changes, Including Self-Harm; Special populations; and ADVERSE REACTIONS).

1.2 Geriatrics

Geriatrics (≥65 years of age): The lowest effective dose of 5 mg/day should always be used as the starting dose in elderly patients (see WARNINGS AND PRECAUTIONS, Bone Fracture Risk, Renal, Hyponatremia, Special Populations, Geriatrics; DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatric; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Geriatrics; and CLINICAL TRIALS, Study Results).

2 CONTRAINDICATIONS

TRINTELLIX (Vortioxetine hydrobromide) is contraindicated in:

- patients who are hypersensitive to vortioxetine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. Angioedema has been reported in patients treated with TRINTELLIX. For a complete listing of excipients, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

- patients with concomitant use of monoamine oxidase inhibitors (MAOIs) (see DRUG INTERACTIONS, Overview; WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Monoamine Oxidase Inhibitors (MAOIs)
Vortioxetine increases serotonergic neurotransmission and must not be used concomitantly in patients taking MAOIs, including linezolid, an antibiotic, methylene blue, a dye used in certain surgeries, or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome or serotonin syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Therefore, at least 14 days should be allowed after discontinuing treatment with a MAOI before starting treatment with vortioxetine.

At least 21 days should elapse after discontinuing vortioxetine treatment before starting a MAOI (see DRUG INTERACTIONS, Overview).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Not Applicable.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **TRINTELLIX (vortioxetine hydrobromide) is not indicated for use in patients below the age of 18 (see WARNINGS AND PRECAUTIONS, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).**

4.2 Recommended Dose and Dosage Adjustment

Adults
The starting and recommended dose of TRINTELLIX is 10 mg vortioxetine once daily for 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, as tolerated. A dose decrease to a minimum of 5 mg vortioxetine once daily may be considered for patients who do not tolerate higher doses.

In clinical trials conducted outside the United States, efficacy was demonstrated with 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day. In the clinical trials conducted in the United States, efficacy was demonstrated with 20 mg/day TRINTELLIX (see CLINICAL TRIALS, Study Results). The efficacy and safety of doses greater than 20 mg/day were not evaluated in controlled clinical trials.

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy beyond response to the acute episode (see CLINICAL TRIALS). During long-term therapy, the dosage should be maintained at the lowest effective level and patients should be periodically reassessed to determine the need to continue treatment.

Geriatric (≥65 years of age)
The lowest effective dose of 5 mg/day vortioxetine should always be used as the starting dose for patients of 65 years of age or older. Caution is advised when treating elderly patients with doses greater than 10 mg/day due to the limited efficacy and safety data from patients of 65 years of age or older that were treated with these doses in controlled clinical trials (see WARNINGS AND PRECAUTIONS, Bone Fracture Risk, Renal, Hyponatremia, Special Populations, Geriatrics; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Geriatrics; and CLINICAL TRIALS, Study Results).

Dosage Adjustment
Patients with Renal Impairment
No dose adjustment is recommended for patients with renal impairment or for patients with end-stage renal disease. However, as with any medicine, caution should be exercised when treating patients with severe renal insufficiency (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Patients with Hepatic Impairment
No dose adjustment is recommended for patients with hepatic impairment.
However, due to extensive hepatic metabolism of vortioxetine, caution is advised when TRINTELLIX is prescribed in patients with moderate or severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Cytochrome P450 Inhibitors
Reduce the dose of TRINTELLIX by half if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to TRINTELLIX treatment (see DRUG INTERACTIONS, Drug-Drug Interactions).

Cytochrome P450 Inducers
Depending on individual patient response, a dose adjustment of TRINTELLIX may be considered if a broad cytochrome P450 inducer (e.g. rifampicin, carbamazepine, phenytoin) is added to TRINTELLIX treatment (see DRUG INTERACTIONS, Drug-Drug Interactions).

Discontinuation of Treatment
Although TRINTELLIX has a relatively long elimination half-life, abrupt discontinuation in placebo-controlled trials was associated with discontinuation symptoms (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Discontinuation Symptoms). Patients should be monitored for discontinuation symptoms when discontinuing treatment with TRINTELLIX. A gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible.

When discontinuing TRINTELLIX, the impact of the elimination half-life of TRINTELLIX (mean elimination half-life of 66 hours) should be considered when drugs that might interact with TRINTELLIX are prescribed (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Elimination).

4.3 Administration

TRINTELLIX should be administered as a single daily dose, with or without food.

4.4 Reconstitution

Not Applicable.

4.5 Missed Dose

If a dose is missed, the next dose should be taken at the usual time. Patients should not take a double dose to make up for a missed dose.

5 OVERDOSAGE

In pre-market clinical studies, the maximum single dose tested was 75 mg in men. Cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX for up to 4 days. In clinical studies that included healthy subjects, ingestion of vortioxetine 40 mg to 75 mg was associated with increased incidences of nausea, postural dizziness, diarrhoea, abdominal discomfort, generalized 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 consider the possibility of multiple drug involvement and should consist of treatment of clinical symptoms and relevant monitoring. Medical follow-up in a specialized environment is recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5, 10, 15, 20 mg	Hydroxypropylcellulose, Hypromellose, Iron oxide red and/or Iron oxide yellow, Macrogol 400, Magnesium stearate, Mannitol, Microcrystalline cellulose, Sodium starch glycolate (type A), Titanium dioxide (E 171)

Each TRINTELLIX tablet contains 6.355, 12.71, 19.065, or 25.42 mg of vortioxetine hydrobromide equivalent to 5, 10, 15, or 20 mg of vortioxetine, respectively.

Film-coated tablet.
5 mg: Pink, almond-shaped, biconvex film-coated tablet engraved with “TL” on one side and “5”

on the other side.
10 mg: Yellow, almond-shaped, biconvex film-coated tablet engraved with “TL” on one side and “10” on the other side.
15 mg: Orange, almond-shaped, biconvex film-coated tablet engraved with “TL” on one side and “15” on the other side.
20 mg: Red, almond-shaped biconvex film-coated tablet engraved with “TL” on one side and “20” on the other side.

Non-medicinal ingredients:
Hydroxypropylcellulose, Hypromellose, Iron oxide red (5, 15 and 20 mg tablets), Iron oxide yellow (10 and 15 mg tablets), Macrogol 400, Magnesium stearate, Mannitol, Microcrystalline cellulose, Sodium starch glycolate (type A), Titanium dioxide (E 171).

Blister: Pack size of 28.

7 WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from Selective Serotonin Reuptake Inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional data

- **There are clinical trials and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm and harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients aged 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behaviours with antidepressants compared to placebo.

Discontinuation Symptoms
At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug such as TRINTELLIX, a gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible. (See ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Discontinuation Symptoms, and DOSAGE AND

ADMINISTRATION, Recommended Dose and Dosage Adjustment, Discontinuation of Treatment).

Bone Fracture Risk

Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs and other newer antidepressants. The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with TRINTELLIX. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long-term treatment with SSRIs and other newer antidepressants including TRINTELLIX, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Dependence/Tolerance

Although vortioxetine has not been systematically studied for its potential for abuse, there was no indication of drug-seeking behaviour in clinical trials with TRINTELLIX. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of TRINTELLIX.

Abrupt discontinuation of TRINTELLIX in placebo-controlled trials was associated with discontinuation symptoms (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Discontinuation Symptoms). Patients should be monitored for discontinuation symptoms when discontinuing treatment with TRINTELLIX. A gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Discontinuation of Treatment).

Driving and Operating Machinery:

Patients should exercise caution when driving or operating hazardous machinery until they are reasonably certain that TRINTELLIX does not adversely affect their ability to engage in such activities (see WARNINGS and PRECAUTIONS, Neurologic).

Hematologic

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of TRINTELLIX and NSAIDs, ASA, or other drugs that affect coagulation (see DRUG INTERACTIONS, Overview). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia).

Hepatic/Biliary/Pancreatic

Hepatic Impairment
Based on studies conducted with TRINTELLIX in patients with mild, moderate or severe hepatic impairment, no dose adjustment is recommended on the basis of hepatic function (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency). However, due to extensive hepatic metabolism of vortioxetine, caution is advised when TRINTELLIX is prescribed in patients with moderate or severe hepatic impairment.

Neurologic
Seizures
Seizures are a potential risk with antidepressant drugs. During short-term clinical trials in patients with Major Depressive Disorder and no history of seizure disorders, seizures were reported in <0.1% of patients that received TRINTELLIX compared to 0% that received placebo. As with other antidepressants, TRINTELLIX should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy. Treatment should be discontinued in any patient who develops seizures or for whom there is an increase in seizure frequency.

Serotonin Syndrome/Neuroleptic Malignant Syndrome
On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with SSRIs and SNRIs, including TRINTELLIX, particularly when given in combination with other serotonergic and/or neuroleptic/antipsychotic drugs. As these syndromes are potentially life-threatening, treatment with TRINTELLIX should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma, and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome TRINTELLIX should not be used in combination with monoamine oxidase inhibitors (MAOIs) [including linezolid, an antibiotic which is a reversible non-selective MAOI and methylthioninium chloride (methylene blue)] or serotonin precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (e.g. triptans, lithium, tramadol, most tricyclic antidepressants), neuroleptics/antipsychotics or St. John's Wort (see CONTRAINDICATIONS and DRUG INTERACTIONS, Overview).

Cognitive and Motor Disturbances
In a study of 21 healthy subjects who were administered single and multiple doses of 10 mg/day TRINTELLIX in the evening, there was no significant impairment, relative to placebo, in mean parameters of driving performance, cognitive function or other psychomotor skills using a battery of neuropsychological tests on the following morning. However, some individuals may show impairment after taking TRINTELLIX (see WARNINGS and PRECAUTIONS, Driving and Operating Machinery).

Ophthalmologic
Angle-Closure Glaucoma
As with other antidepressants, TRINTELLIX can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric
Suicide

The possibility of a suicide attempt is inherent in major depressive disorder (MDD) and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high risk patients. The smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug (see WARNINGS AND PRECAUTIONS, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Activation of Mania/Hypomania
Mania/hypomania was reported for <0.1% (1 out of 3904) of patients treated with TRINTELLIX in short-term Phase 2/3 trials in patients with Major Depressive Disorder. TRINTELLIX should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase. A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Aggression/agitation
Patients treated with antidepressants, including vortioxetine, may experience feelings of aggression, anger, agitation and irritability. Patient's condition and disease status should be closely monitored. Patients (and caregivers of patients) should be alerted to seek medical advice, if aggressive/agitated behaviour emerges or aggravates.

Electroconvulsive Therapy (ECT)
The safety and efficacy of the concurrent use of TRINTELLIX and ECT have not been studied, and therefore, caution is advisable.

Renal
Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of antidepressants with serotonergic effect (SSRIs, SNRIs). Caution should be exercised in patients at risk, such as elderly, cirrhotic patients, patients concomitantly treated with medications known to cause hyponatraemia (e.g. diuretics), or patients who are otherwise volume depleted. Discontinuation of TRINTELLIX should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Symptoms may include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls.

Renal Impairment
Based on a study conducted with TRINTELLIX in patients with mild, moderate, severe and end stage renal impairment no clinically significant pharmacokinetic changes were observed. Subsequently, no dosage adjustment is needed, however as with any medicine, caution should be exercised when treating patients with severe renal insufficiency (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Patients with Renal Impairment and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of TRINTELLIX in human pregnancy has not been established. Therefore, TRINTELLIX should not be used during pregnancy or in women intending to become pregnant, unless the benefit outweighs the possible risk to the fetus.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant. If TRINTELLIX is used until or shortly before birth, discontinuation symptoms in the newborn should be considered.

Animal studies did not demonstrate a teratogenic effect of vortioxetine, but lower fetal weight and delayed ossification were seen in rats at systemic exposures corresponding to approximately 6 times the C_{max} at the maximum recommended human dose (20 mg/day) and in rabbits at subtherapeutic exposures (see NON-CLINICAL TOXICOLOGY).

Post-marketing reports indicate that some neonates exposed to SNRIs, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included: 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 are consistent with either a direct toxic effect of SNRIs, SSRIs, or other newer antidepressants, or, possibly a drug discontinuation syndrome. In a majority of instances, such complications begin immediately or soon (<24 hours) after delivery. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. When treating a pregnant woman with TRINTELLIX during later stages of pregnancy, the physician should carefully consider the potential risks and benefits of treatment.

Epidemiological studies on persistent pulmonary hypertension in the newborn (PPHN) have shown that the use of SSRIs in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy (Odds Ratio 6.1, 95% CI 2.2-16.8). A study using data from the Swedish Medical Birth Register for 831,324 infants born in 1997-2005 found an increased risk of PPHN of approximately 2-fold associated with patient-reported maternal use of SSRIs in the first trimester of pregnancy (Risk Ratio 2.4, 95% CI 1.2-4.3), and an increased risk of PPHN of approximately 4-fold associated with a combination of patient-reported maternal use of SSRIs in the first trimester and an antenatal SSRI prescription in later pregnancy (Risk Ratio 3.6, 95% CI 1.2-8.3). Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk cannot be ruled out considering the mechanism of action (increase in serotonin concentrations).

7.1.2 Breast-feeding

Available data in animals have shown excretion of vortioxetine/vortioxetine metabolites in milk. It is expected that TRINTELLIX will be excreted into human milk. Because a risk to the nursing

child cannot be excluded, breast-feeding is not recommended during treatment with TRINTELLIX.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from TRINTELLIX treatment, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the efficacy of Trintellix in adolescents aged 12 to 17 years have not been demonstrated. The safety and efficacy in children aged 7 to 11 years has not yet been established. Therefore, TRINTELLIX is not indicated for use in patients below the age of 18. In general, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults except for higher incidences of suicidal ideation reported (see WARNINGS AND PRECAUTIONS, Potential Association With Behavioural And Emotional Changes, Including Self-Harm; ADVERSE REACTIONS).

7.1.4 Geriatrics

As with any medicine, in the context of a greater potential for other concomitant medical conditions and drug therapies in elderly patients, caution should be exercised when treating the elderly. Based on the available efficacy and safety data from placebo controlled clinical trials, a dosage adjustment is recommended for elderly patients (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatrics; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Geriatrics; and CLINICAL TRIALS, Study Results).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse events information for TRINTELLIX (vortioxetine hydrobromide) was collected in adult patients with MDD in a clinical programme that included more than 6,700 patients, of whom 3,460 were treated with TRINTELLIX (5 to 20 mg/day) in short-term placebo-controlled (up to 8 weeks) studies. During clinical trials, all treatment groups were comparable with respect to gender, age and race. The mean age of patients was 46 years (18 to 88 years). Of these patients, approximately 67% were women and 33% were men.

The most commonly observed adverse events in MDD patients treated with TRINTELLIX in 6 to 8-week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting. The majority of cases of nausea in the MDD Short-Term Pool were transient (median duration ranged from 9 to 16 days) and mild to moderate, but some led to discontinuation of treatment (see below). The incidence of nausea was highest during the first week of treatment. Approximately 10% of TRINTELLIX-treated patients had nausea at the end of the 6 or 8 week treatment, compared to 2% of placebo-treated patients.

Adverse Events Leading to Discontinuation of Treatment
From the short-term (up to 8-weeks) placebo-controlled studies, discontinuation due to adverse events was more common with TRINTELLIX (6.0%) compared with placebo (4.0%).

Nausea was the most common reason for patients discontinuing due to adverse events. In the short-term MDD placebo-controlled studies, the incidence of nausea leading to withdrawal in patients who received TRINTELLIX 5 mg, 10 mg, 15 mg and 20 mg was 1.1%, 1.4%, 3.8% and 3.3%, respectively, compared to 0.3% for placebo. Withdrawing due to nausea was highest during the initial weeks of treatment.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions in MDD Clinical Trials

Table 2 enumerates the incidence of treatment emergent adverse events that occurred in 3,460 depressed patients who received TRINTELLIX at doses ranging from 5 to 20 mg/day in placebo-controlled trials (of up to 8 weeks in duration). Events included are those occurring in 1% or more of patients treated with TRINTELLIX, and for which the incidence in patients treated with TRINTELLIX was greater than the incidence in placebo-treated patients. Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1.

Table 2
Incidence of common adverse events* for Major Depressive Disorder, pool of 12 short-term studies

Body System/Adverse Event	Percentage of Patients Reporting				
	Placebo (n = 1968)	TRINTELLIX 5 mg/day (n =1157)	TRINTELLIX 10 mg/day (n =1042)	TRINTELLIX 15 mg/day (n =449)	TRINTELLIX 20 mg/day (n =812)
Gastrointestinal Disorders					
Nausea	8.1	20.5	22.6	31.2	27.2
Diarrhoea	5.5	6.6	5.4	9.4	5.5
Dry mouth	5.6	6.4	5.5	6.0	6.5
Constipation	2.9	3.4	3.6	5.6	4.4
Vomiting	1.1	2.7	3.6	6.5	4.4
Dyspepsia	1.9	1.8	1.7	2.4	2.1
Flatulence	1.2	1.0	1.9	2.0	0.9
Abdominal discomfort	1.1	1.4	0.6	2.0	1.6
General Disorders and Administration Site Conditions					
Fatigue	2.7	3.1	2.8	3.6	2.6
Infections and Infestations					
Nasopharyngitis	3.9	5.3	4.0	3.6	4.9
Metabolism and Nutrition Disorders					
Decreased appetite	1.0	2.1	0.7	0.7	1.6
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	0.9	0.9	0.9	1.8	1.1
Nervous System					
Dizziness	5.3	5.5	5.2	7.1	6.3
Somnolence	2.3	3.3	2.9	2.7	3.3
Sedation	0.6	1.2	0.5	1.3	1.5
Psychiatric Disorders					
Insomnia	2.5	3.1	2.6	1.8	2.7
Abnormal dreams	0.8	0.4	0.5	1.6	1.4
Skin and Subcutaneous Tissue Disorders	1.7	2.3	2.3	1.8	0.7
Hyperhidrosis	0.4	0.4	1.3	1.6	1.8
Pruritus generalised					

* Events included are those occurring in 1% or more of patients treated with TRINTELLIX, and for which the incidence in patients treated with TRINTELLIX was greater than the incidence in placebo-treated patients.

Male and Female Sexual Dysfunction

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be a consequence of pharmacologic

treatment.

The incidence of self-reported adverse sexual reactions was low and similar to placebo in clinical short- and long-term studies with vortioxetine (5 to 20 mg/day). Table 3 shows the percentage of voluntarily reported adverse reactions related to sexual function in the short-term placebo-controlled studies in patients with MDD. Reported adverse events were classified using MedDRA, version 14.1.

Table 3
Incidence of sexual dysfunction adverse reactions in a pool of 12 placebo-controlled clinical trials
For Major Depressive Disorder

Adverse Event	Percentage of Patients Reporting	
	TRINTELLIX (5-20 mg) (n =3460)	**Placebo (n = 1968)**
Libido decreased	0.7	0.6
Orgasm abnormal	0.3	0.2
Anorgasmia	0.2	0.0
Loss of libido	0.2	0.0
Disturbance in sexual arousal	<0.1	0.0
Orgasmic sensation decreased	<0.1	<0.1
Sexual dysfunction	<0.1	<0.1
In Males only[1]		
Ejaculation delayed	0.5	0.1
Erectile dysfunction	0.3	0.4
Ejaculation disorder	<0.1	0.0
In Females only[2]		
Vulvovaginal dryness	<0.1	0

[1]Denominator used was for males only (n=1153 for TRINTELLIX; n=702 for Placebo).
[2]Denominator used was for females only (n=2307 for TRINTELLIX; n=1266 for Placebo).

Because voluntarily reported adverse sexual reactions are presumed to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 7 short-term placebo-controlled studies; 6 studies in patients with MDD and 1 study in patients with Generalized Anxiety Disorder.

The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction. Each item is rated from 1 to 6, with higher scores indicating greater dysfunction. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4. For patients without sexual dysfunction at baseline, the incidence of treatment-emergent sexual dysfunction on the ASEX is show in Table 4 below. TRINTELLIX was associated with higher incidences of treatment-emergent sexual dysfunction compared to placebo, when evaluated by the ASEX scale.

Physicians should routinely inquire about possible sexual side effects during treatment with TRINTELLIX.

Table 4
Incidence (n/N)* of treatment-emergent sexual dysfunction based on ASEX in a pool of 7 placebo-controlled clinical trials

	TRINTELLIX (5 mg)	TRINTELLIX (10 mg)	TRINTELLIX (15 mg)	TRINTELLIX (20 mg)	Placebo
Females	N=65 22%	N=94 23%	N=57 33%	N=67 34%	N=135 20%
Males	N=67 16%	N=86 20%	N=67 19%	N=59 29%	N=162 14%

*incidence based on n=number of subjects with treatment-emergent ASEX sexual dysfunction at 2 consecutive visits/ N=number of subjects without sexual dysfunction at baseline.

Discontinuation Symptoms
Discontinuation symptoms were evaluated in 7 placebo-controlled trials (6 short-term and 1 long-term) during a two-week period following abrupt discontinuation of TRINTELLIX. In 4 of the short-term studies (8-weeks), the Discontinuation-Emergent Signs and Symptoms (DESS) Checklist was also used. Abrupt discontinuation of vortioxetine was associated with increased frequency of discontinuation-emergent adverse events and in the frequency of signs and symptoms in the DESS checklist, as compared to placebo. The most common symptoms associated with discontinuation were headache, increased dreaming/nightmares, mood swings, muscle tension/stiffness, sudden outbursts of anger, dizziness/vertigo and nose running. Patients should be monitored for discontinuation symptoms when discontinuing treatment with TRINTELLIX

When discontinuing TRINTELLIX, a gradual reduction in the dose, rather than an abrupt cessation, is recommended whenever possible (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Discontinuation of Treatment).

Weight Changes
TRINTELLIX had no clinically meaningful effect on body weight as measured by the mean change from baseline in the long-term (24-64 weeks) and short-term (6-8 weeks) placebo-controlled studies. The mean changes in weight in a long-term placebo-controlled study in patients with MDD was +0.4 kg in the TRINTELLIX 5 or 10 mg/day group and +0.1 kg in placebo group. The proportions of patients with a weight gain ≥7% were 6.5 % in the TRINTELLIX 5 or 10 mg/day group and 5.8% in the placebo group. The proportions of patients with a weight decrease ≥7% were 3.5% in the TRINTELLIX 5 or 10 mg/day group and 2.6% in the placebo group.

Cardiovascular Parameters
TRINTELLIX and placebo groups in MDD patients were compared with respect to mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The analyses did not reveal any clinically important changes in blood pressure or heart rate associated with TRINTELLIX treatment.

In a randomized, placebo- and positive-controlled, parallel group, thorough QTc study in 340

healthy subjects, changes in maximum mean systolic blood pressure of 2.8 mmHg (90% CI 0.7, 4.8) for TRINTELLIX 10 mg/day and 4.8 mmHg (90% CI 2.7, 7.0) for TRINTELLIX 40 mg/day were observed after 14 days treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Electrocardiography and Hemodynamics).

In the pooled short-term studies in MDD, the mean change in systolic blood pressure from baseline to last assessment was -0.35 mmHg for all vortioxetine doses combined and -1.0 mmHg for placebo. For vortioxetine 20 mg alone the mean change was +0.35 mmHg. In a study in elderly patients with MDD, the mean change in systolic blood pressure from baseline to last assessment was -1.1 mmHg for vortioxetine and -3.9 mmHg for placebo. Vortioxetine was *not* associated with increased incidence of individual potentially clinically significant (PCS) changes in blood pressure in the short-term MDD studies.

Electrocardiograms
TRINTELLIX has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential in clinical studies. In a randomized, placebo- and positive-controlled, parallel group, thorough QTc study in 340 healthy subjects, treatment with TRINTELLIX 10 or 40 mg/day for 14 days did not prolong QT/QTc intervals, and there was no plasma concentration-QTc relationship observed.

In the thorough QTc study in healthy subjects, treatment with TRINTELLIX 10 or 40 mg/day for 14 days was associated with modest decreases in heart rate of -4.7 bpm (90% CI -6.8, -2.7) for 10 mg/day and -5.4 bpm (90% CI -7.4, -3.4) for 40 mg/day after 14 days treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Electrocardiography and Hemodynamics).

In the pooled short-term studies in MDD, the mean change in ECG heart rate from baseline to last assessment was -0.06 bpm for all vortioxetine doses combined and +0.9 bpm for placebo. For the individual vortioxetine doses the mean changes were -0.02 (5 mg), -0.4 (10 mg), -0.24 (15 mg), and +0.38 (20 mg). In a study in elderly patients with MDD, the mean change in ECG heart rate from baseline to last assessment was -1.55 bpm for vortioxetine and -0.23 bpm for placebo. Vortioxetine was *not* associated with increased incidence of individual potentially clinically significant (PCS) changes in ECG heart rate in the short-term MDD studies.

Adverse Events During Treatment up to 64 weeks in MDD
The adverse event profile of TRINTELLIX in a long-term study in patients with MDD was similar to that observed in short-term studies.

Patients who were remitters following 12 weeks of acute, open-label treatment with TRINTELLIX were observed for relapse during a double-blind, placebo-controlled treatment period (see CLINICAL TRIALS, Trial Design and Study Demographics). Because the double-blind period was planned to end simultaneously for all patients, the planned duration of treatment ranged from a minimum of 24 weeks to up to 64 weeks, depending on the time of enrollment. During the long-term, double-blind treatment period the overall incidence of Treatment-Emergent Adverse Events (TEAEs) was 62% for TRINTELLIX and 64% for placebo. Table 5 enumerates the incidence of TEAEs that occurred in 204 depressed patients who received TRINTELLIX at 5 or 10 mg/day for up to 24 to 64 weeks. Events included are those occurring in 2% or more of patients treated with TRINTELLIX, and for which the incidence in patients treated with TRINTELLIX was greater than the incidence in placebo-treated patients. Reported adverse events were classified using MedDRA, version 12.0.

Table 5
Incidence of adverse events ≥2%[1]
in remitted patients with MDD receiving double-blind
treatment for up to 24 to 64 weeks[2]

Adverse Event	Percentage of Patients Reporting	
	TRINTELLIX 5 or 10 mg (n =204)	**Placebo (n = 192)**
Nausea	8.8	3.1
Gastroenteritis	5.4	3.1
Abdominal pain upper	4.9	1.0
Insomnia	2.5	1.6
Dry mouth	2.0	0.0
Cough	2.0	0.5
Asthenia	2.0	0.5
Influenza-like illness	2.0	1.0
Myalgia	2.0	0.5
Urinary tract infection	2.0	0.5

[1]Events included are those occurring in 2% or more of patients treated with TRINTELLIX (5 or 10 mg/day), and for which the incidence was greater than the incidence in placebo-treated patients.
[2]Median duration of the double-blind treatment was 27 weeks for placebo and 28 weeks for TRINTELLIX (5 or 10 mg/day).

8.3 Less Common Clinical Trial Adverse Reactions

The events listed below present treatment emergent adverse events occurring in less than 1% of the patients treated with TRINTELLIX (5 to 20 mg/day) in 12 short-term placebo-controlled studies in depressed patients. The listing does not include events: 1) already listed in previous tables or elsewhere in labelling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

The reported adverse events were classified using MedDRA, version 14.1. The events are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in less than 1/1,000 patients.

Blood and Lymphatic System Disorders
Rare: Leukopenia

Cardiac Disorders
Infrequent: Sinus bradycardia, angina pectoris
Rare: Ventricular extrasystoles

Ear and Labyrinth Disorders

Infrequent: Vertigo

Eye Disorders
Infrequent: Dry eye, visual impairment
Rare: Visual acuity reduced, vitreous floaters, eye pain, mydriasis (which may lead to acute narrow angle glaucoma)

Gastrointestinal Disorders
Infrequent: Abdominal distension, gastritis, epigastric discomfort, salivary hypersecretion
Rare: Aphthous stomatitis, eructation, glossitis, bowel movement irregularity, cheilitis, colitis, haematochezia

General Disorders and Administration Site Conditions
Infrequent: Chest discomfort, malaise, non-cardiac chest pain

Hepatobiliary Disorders
Rare: Hepatic function abnormal

Immune System Disorders
Rare: Hypersensitivity

Investigations
Infrequent: Weight increased, electrocardiogram QT prolonged, heart rate increased, low density lipoprotein increased, blood cholesterol increased, blood triglycerides increased, blood creatine phosphokinase increased, blood gamma-glutamyltransferase increased
Rare: Blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased

Metabolism and Nutrition Disorders
Infrequent: Dehydration
Rare: Hyperglycaemia, dyslipidaemia, glucose tolerance impaired, hypoglycaemia

Nervous System
Infrequent: Dysgeusia, lethargy, tremor, myoclonus, hypersomnia, restless legs syndrome, memory impairment
Rare: Ageusia, psychomotor hyperactivity, convulsion, hyperreflexia, muscle contractions involuntary, sensory disturbance, formication

Psychiatric Disorders
Infrequent: Tension, bruxism, restlessness, derealisation, depersonalization
Rare: Suicide attempt, terminal insomnia, euphoric mood

Renal and Urinary Disorders
Infrequent: Micturition urgency, nocturia
Rare: Urine odour abnormal

Reproductive System and Breast Disorders
Infrequent: Menstruation delayed, polymenorrhoea, breast tenderness

Respiratory, Thoracic and Mediastinal Disorders
Infrequent: Yawning

Rare: Respiratory tract congestion, dry throat

Skin and Subcutaneous Tissue Disorders
Infrequent: Pruritus, night sweats, rash, urticaria
Rare: Dermatitis allergic, psoriasis, rash erythematous, skin irritation

Vascular Disorders
Infrequent: Hypertension, flushing
Rare: Hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not Applicable.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Clinical Trial Adverse Events in Pediatric patients with depressive or anxiety disorder:
A total of 308 pediatric patients (ages 12-17 years) with a diagnosis of major depressive disorder (MDD) were treated in a randomised, double-blind, placebo-controlled, active referenced, fixed dose, 8-week study. Although efficacy could not be established, the adverse reaction profile of vortioxetine in adolescents was similar to that seen for adults. The most commonly reported adverse events in the vortioxetine treatment groups were nausea, vomiting and headache. The most common adverse events leading to discontinuation were suicidal ideation, nausea and vomiting.
The pharmacokinetics, safety and tolerability of vortioxetine 5-20 mg per day was assessed in 48 pediatric patients (ages 7-17 years) with a diagnosis of depressive or anxiety disorder in an open-label trial, which consisted of a main study period of 14 days and a 6-month extension period. Adverse events reported with an incidence of ≥10% during the main or during the extension study period were headache, nausea, sedation, abdominal pain upper, fatigue, vomiting and dysmenorrhoea. TRINTELLIX is not indicated for use in patients below the age of 18 (see also WARNINGS AND PRECAUTIONS, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

8.6 Post-Market Adverse Reactions

The following adverse events have been identified during post-approval use of TRINTELLIX. These events are reported voluntarily from a population of uncertain size, and it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal system
Acute pancreatitis

Immune system disorders
Anaphylactic reaction

Nervous system disorders
Serotonin syndrome

Psychiatric disorders
Agitation, aggression

Skin and subcutaneous tissue disorders
Angioedema

Vascular disorders
Haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal haemorrhage)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs)
(see CONTRAINDICATIONS)

9.2 Overview

Vortioxetine is extensively metabolized, primarily through oxidation and subsequent glucuronic acid conjugation. *In vitro*, the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite. Caution is recommended when TRINTELLIX is co-administered with drugs that are mainly metabolized by CYP2D6, particularly those that have a narrow therapeutic index (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism).

Vortioxetine was highly bound to plasma protein *in vitro* (>99%) therefore administration of TRINTELLIX to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects may result from displacement of protein bound vortioxetine by other tightly bound drugs.

Monoamine Oxidase Inhibitors (MAOIs)
Combined use of TRINTELLIX and MAOIs is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Neurologic Serotonin Syndrome/Neuroleptic Malignant Syndrome). In patients receiving SSRIs in combination with a MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes, including extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome. TRINTELLIX should not be used in combination with a MAOI, (including linezolid, an antibiotic which is a reversible non-selective MAOI, and methylene blue, which is a MAOI) or within 14 days of discontinuing treatment with a MAOI.

Similarly, at least 21 days should elapse after discontinuing TRINTELLIX treatment before starting a MAOI (see CONTRAINDICATIONS).

Serotonergic Medicinal Products
Based on the mechanism of action of TRINTELLIX and the potential for serotonin syndrome, caution is advised when TRINTELLIX is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, St. John's Wort, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome). Concomitant use of TRINTELLIX and MAOIs (including linezolid and methylene blue), is contraindicated (see CONTRAINDICATIONS).

Triptans ($5HT_1$ agonists)
Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs/SNRIs and triptans. If concomitant treatment with TRINTELLIX and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Drugs Affecting Platelet Function (e.g. NSAIDs, ASA and other anticoagulants)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when TRINTELLIX is initiated or discontinued. (See WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

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), mefloquin, bupropion and tramadol) (see WARNINGS AND PRECAUTIONS, Neurologic, Seizures).

Lithium and tryptophan
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.

Alcohol
No effect on the pharmacokinetics of vortioxetine or ethanol and no significant impairment, relative to placebo, in cognitive function was observed when vortioxetine in a single dose of 20 mg or 40 mg was co-administered with a single dose of 0.6 g/kg ethanol in healthy subjects. However, alcohol intake is not advisable during antidepressant treatment.

Other CNS-Active Drugs

The risk of using TRINTELLIX in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of TRINTELLIX and such drugs is required.

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 - Established or Potential Drug-Drug Interactions

	Source of Evidence	**Effect**	**Clinical comment**
Bupropion	CT	The exposure of vortioxetine increased 2.3-fold for 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 events when bupropion was added to vortioxetine than when vortioxetine was added to bupropion.	Reduce the dose of vortioxetine by half if strong CYP2D6 inhibitors (e.g. bupropion, cinacalcet, quinidine, fluoxetine, paroxetine) are co-administered (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Cytochrome P450 Inhibitors).
Ketoconazole and Fluconazole	CT	When a single dose of 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 vortioxetine dose adjustment is needed.
Omeprazole	CT	No inhibitory effect of 40 mg single-dose omeprazole (CYP2C19 inhibitor) was observed on the multiple-dose pharmacokinetics of vortioxetine in healthy subjects.	No vortioxetine dose adjustment is needed

	Source of Evidence	**Effect**	**Clinical comment**
CYP2D6 Poor Metabolizers	T	Co-administration of strong inhibitors of CYP3A4 (such as itraconazole, voriconazole, clarithromycin, telitromycin, nefazodone and many of the HIV protease inhibitors) and inhibitors of CYP2C9 (such as fluconazole and amiodarone) to CYP2D6 poor metabolizers has not been investigated specifically.	It is anticipated that such co-administration will lead to increased exposure of vortioxetine in these patients and vortioxetine dosage adjustment may be required (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Genetic Polymorphism (CYP2D6 Poor Metabolizers).
Rifampicin	CT	When a single dose of 20 mg vortioxetine was co-administered following 10 days of rifampicin 600 mg/day (an inducer of CYP isozymes) in healthy subjects, a 72% decrease in AUC of vortioxetine was observed.	Depending on individual patient response, a vortioxetine dose adjustment may be considered if a broad cytochrome P450 inducer (e.g. rifampicin, carbamazepine, phenytoin) is added to vortioxetine treatment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Cytochrome P450 Inducers).
Substrates of CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinyl estradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or CYP2D6 (dextromethorphan)	CT	Multiple doses of vortioxetine in healthy subjects had no clinically significant effects on plasma concentrations of known substrates of CYP2C19 (omeprazole, diazepam), CYP3A4/5 (ethinyl estradiol, midazolam), CYP2B6 (bupropion), CYP2C9 (tolbutamide, S-warfarin), CYP1A2 (caffeine) or CYP2D6 (dextromethorphan).	No dose adjustment of these substrates is needed.

	Source of Evidence	Effect	Clinical comment
Diazepam	CT	No significant pharmacodynamic interactions or cognitive impairments were observed following co-administration of vortioxetine with a single 10 mg dose of diazepam.	No vortioxetine dose adjustment is needed.
Oral contraceptive	CT	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) for 21 days.	No vortioxetine dose adjustment is needed.
Lithium	CT	No clinically relevant effect was observed during steady-state lithium exposure following co-administration with vortioxetine 10 mg/day for 14 days in healthy subjects.	Concomitant use of vortioxetine with lithium should be undertaken with caution (see DRUG INTERACTIONS, Overview).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.4 Drug-Food Interactions

No effect from food on the pharmacokinetics of vortioxetine was observed (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

9.5 Drug-Herb Interactions

St. John's Wort
Concomitant use of antidepressants with serotonergic effect and herbal remedies containing St. John´s Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions including serotonin syndrome (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

9.6 Drug-Laboratory Test Interactions

Interference with urine drug screen
There have been reports of false positive results in urine enzyme immunoassays for methadone in patients who have taken vortioxetine. Caution should be exercised in the interpretation of positive urine drug screen results, and confirmation by an alternative analytical technique (e.g., chromatographic methods) should be considered

9.7 Drug-Lifestyle Interactions

Not Applicable.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The antidepressant effect of vortioxetine is thought to be related to modulation of serotonergic neurotransmission in the CNS through mechanisms that include inhibition of reuptake of serotonin (5-HT) at the 5-HT transporter (5-HT_T) and activity at several human 5-HT receptors, including 5-HT_{1A} receptor agonism, 5-HT_{1B} receptor partial agonism, and 5-HT_3, 5-HT_{1D} and 5-HT_7 receptor antagonism. The precise contribution of the individual targets to the net effect of vortioxetine and the exact mechanism of action is not fully understood.

10.2 Pharmacodynamics

In vitro, vortioxetine binds with high affinity to the human 5-HT transporter (5-HT_T) (Ki = 1.6 nM) and inhibits reuptake of serotonin (IC50 = 5.4 nM). Lower affinity binding was observed at the human norepinephrine (Ki = 113 nM) and human dopamine (Ki > 1000 nM) transporters.

Vortioxetine binds *in vitro* to the human 5-HT_3 (Ki = 3.7 nM), 5-HT_{1A} (Ki = 15 nM), 5-HT_7 (Ki = 18 nM), 5-HT_{1B} (Ki = 33 nM) and 5-HT_{1D} (Ki = 54 nM) receptors. Vortioxetine has antagonist activity at the human 5-HT_3, 5-HT_{1D} and 5-HT_7 receptors (cIC50 = 3.5 nM, 25 nM, and 450 nM respectively), partial agonist activity at the human 5-HT_{1B} receptor (EC50 = 120 to 460 nM), and agonist activity at the human 5-HT_{1A} receptor (EC50 = 199 nM). The role of these activities in the antidepressant effect of vortioxetine has not been established.

In humans, two positron emission tomography (PET) studies 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 indicated that mean 5-HT transporter occupancy was approximately 50% at 5 mg/day, 65% at 10 mg/day and approximately 80% at 20 mg/day in the specific regions of interest.

10.3 Pharmacokinetics

The pharmacological activity of vortioxetine is due to the parent drug. The pharmacokinetics are linear and time-independent in the dose range studied (2.5 to 60 mg/day). Steady state plasma levels are achieved in approximately 2 weeks.

Table 7
Summary of TRINTELLIX's Pharmacokinetic Parameters in Young Healthy Adult Male Subjects

Mean	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	Clearance (L/h)	Volume of distribution (L)
Single dose						
10 mg (N=6)	2.70	8.00	282	N/A	50.67[a]	3697
20 mg (N=6)	5.69	8.00	349	N/A	62.42	3871

Table 7 Summary of TRINTELLIX's Pharmacokinetic Parameters in Young Healthy Adult Male Subjects						
Mean	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{0-inf} (ng.h/mL)**	**AUC_{0-24h} (ng.h/mL)**	**Clearance (L/h)**	**Volume of distribution (L)**
Multiple dose						
20 mg (N=6)	19.21	7.00	N/A	361	61.85	4340

[a] N = 5 for Clearance; N/A= not applicable

Following single doses of vortioxetine to young adult women and elderly men and women, the pharmacokinetic parameters of vortioxetine were generally consistent with the values observed in young adult men (Table 7). Following multiple doses of vortioxetine, there was an increase in the exposure of vortioxetine in healthy elderly subjects compared to young healthy adult subjects. C_{max}, AUC_{0-24h}, and elimination half-life ($t_{1/2}$) were increased and oral clearance was decreased in elderly subjects compared to young adult subjects (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics ; DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Geriatric; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

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, and 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.

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

Metabolism: Vortioxetine is extensively metabolized, primarily through oxidation and subsequent glucuronic acid conjugation.

In vitro, the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite.

Vortioxetine did not inhibit CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 *in vitro.* Vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. *In vitro* vortioxetine is not a substrate or inhibitor of the P-gp transporter (see DRUG INTERACTIONS).

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 unchanged vortioxetine are excreted in the urine.

Special Populations and Conditions

Pediatrics: TRINTELLIX is not indicated for use in patients below the age of 18 (see INDICATIONS AND CLINICAL USE: Pediatrics; WARNINGS AND PRECAUTIONS, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

Pharmacokinetics of vortioxetine in paediatric patients with major depressive disorder following oral administration of 5 to 20 mg once daily was characterized using population modelling analyses based on data from a pharmacokinetic study (7-17 years) and an efficacy and safety study (12-17 years). The pharmacokinetics of vortioxetine in ~~pa~~ediatric patients were similar to that observed in adult patients.

Geriatrics: In elderly healthy subjects (≥65 years; n=20), the exposure of vortioxetine increased up to 27% (C_{max} and AUC) compared to young healthy adult control subjects (≤45 years) after multiple doses of 10 mg/day. A higher frequency of gastrointestinal adverse events was reported in elderly subjects compared to young adult subjects (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage adjustment, Geriatric).

Sex: Systemic exposures between males and females are similar and no dose adjustment is needed.

Genetic Polymorphism (CYP2D6 Poor Metabolizers): The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolizers than in extensive metabolizers. In the presence of strong CYP3A4/2C9-inhibitors, the exposure could potentially be higher and a dosage adjustment may be required (see DRUG INTERACTIONS, Drug-Drug Interactions).

Ethnic origin: No dose adjustment on the basis of race or ethnicity is needed. Race or ethnicity had no apparent effect on the pharmacokinetics of vortioxetine.

Hepatic Insufficiency: The pharmacokinetics in subjects (N = 6-8) with mild, moderate, or severe hepatic impairment (Child-Pugh Criteria A, B, or C, respectively) were compared to healthy volunteers. After doses of 10 mg (mild and moderate) or 5 mg (severe), the changes in AUC were less than 10% in subjects with mild or moderate hepatic impairment, and 44% higher in those with severe hepatic impairment while the Cmax was 24% lower. No dose adjustment is needed on the basis of hepatic function, however, caution should be exercised (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS).

Renal Insufficiency: Following a single dose of 10 mg vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, and severe; n=8 per group) caused modest exposure increases (up to 30%), compared to healthy matched controls.

No dose adjustment is needed on the basis of renal function, however, caution should be exercised (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS).

Electrocardiography and Haemodynamics:
Vortioxetine was assessed for effects on ECG parameters and blood pressure in a randomised, double-blind, placebo- and positive-controlled, 4-arm parallel group study performed in healthy male volunteers (N=82/treatment arm). Vortioxetine was tested at a therapeutic dose of 10 mg per day for 14 days and a supratherapeutic dose of 40 mg per day for 14 days. ECG data were assessed at 0 h, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 23.5 h post-dose on day 14.

At the therapeutic dose of 10 mg per day, the maximum mean difference from placebo using QTcFm (QTcFm = QT+ 0.154[1- RR]) was 4.0 ms (90% CI 1.3, 6.7) at 4 h. At the dose of 40 mg per day, the maximum mean difference from placebo using QTcFm was 4.6 ms (90% CI 2.2, 7.1) at 4 h. No noteworthy effects on the PR interval or QRS duration were observed in this study.

Vortioxetine was observed to have a modest negative chronotropic effect. The maximum mean decrease observed in heart rate was of -4.7 bpm (90% CI -6.8, -2.7) for 10 mg per day and -5.4 bpm (90% CI -7.4, -3.4) for 40 mg per day on Day 14.

Supine systolic blood pressure was increased by vortioxetine. The maximum mean increase observed in systolic blood pressure was of 2.8 mmHg (90% CI 0.7, 4.8) for 10 mg per day and 4.8 mmHg (90% CI 2.7, 7.0) for 40 mg per day on Day 14. No noteworthy effects on diastolic blood pressure were observed in this study.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15° - 30°C) protected from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

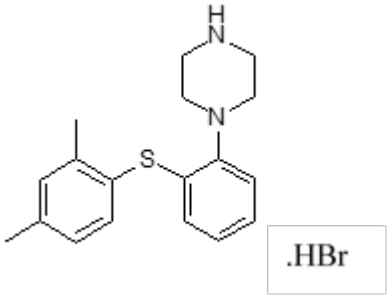
Drug Substance

Proper name: Vortioxetine hydrobromide

Chemical name: 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide

Molecular formula and molecular mass: $C_{18}H_{22}N_2S$, HBr
379.36 g/mole

Structural formula:



Physicochemical properties: The drug substance is a white to very slightly beige powder.

Slightly soluble in water; at ambient temperature solubility is measured to approximately 1.3 mg base/mL, pH being 5.5 in the saturated solution. At pH = 7.4 the solubility is approximately 50 µg base/mL.

Melting point: = 231°C
pKa= 9.1 (±0.1) and 3.0 (±0.2)

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Short-term studies
More than 3,000 patients were treated with TRINTELLIX (vortioxetine hydrobromide tablet) in short-term MDD studies (of up to 8 weeks duration) as listed in Table 8.

The efficacy of TRINTELLIX 5 mg, 10 mg, 15 mg, and 20 mg once daily in the treatment of MDD was evaluated in ten short-term, randomized, double-blind, placebo-controlled studies in adults, and one short-term placebo-controlled study in elderly patients. All studies included male and female inpatients and outpatients, who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. The studies in adults included patients 18 to 75 years old (mean age range 43 to 47 years) with baseline total scores on the Montgomery Asberg Depression Rating Scale (MADRS) $\geq$ 26 in seven studies, $\geq$ 30 in two studies and $\geq$ 22 in one study. The study of elderly patients included patients who were 65 years of age or older (range

64 to 88 years), with at least one previous major depressive episode before 60 years of age, a baseline MADRS total score ≥ 26 and no comorbid cognitive impairment (Mini Mental State Examination score ≥ 24 at screening). Approximately two-thirds of the patients included in the short-term studies were female.

All short-term studies were of similar design. Patients received fixed doses of TRINTELLIX 5 mg, 10 mg, 15 mg or 20 mg once daily for 6 or 8 weeks (two 6-week studies, nine 8-week studies). Six of the studies, including the study in elderly patients, included an active reference (SNRI) comparator arm. The primary outcome measure was the mean change from baseline to Week 6/Week 8 in the MADRS total score (seven studies) or the 24-item Hamilton Rating Scale for Depression (HAM-D_{24}) (four studies). Five of the studies in adults were conducted in countries outside the United States (non-US) and five were conducted only in the United States (US). The study in elderly patients included patients from non-US countries and from the US.

Long-term maintenance of effect study

The efficacy of TRINTELLIX in maintaining an antidepressant effect was assessed in a non-US trial including adult patients with MDD who initially responded to 12 weeks of acute open-label treatment with TRINTELLIX. Patients in this study were 18 to 75 years of age, inpatients or outpatients who met DSM-IV-TR criteria for MDD and had a baseline MADRS total score ≥ 26.

During the 12-week open label, acute treatment period patients received TRINTELLIX 5 mg/day for the first 2 weeks. The dose could be increased to a 10 mg/day between Weeks 3 and 8 and decreased again to 5 mg/day during that time if needed. From Weeks 8 to 12 the dose remained fixed at 5 mg/day or 10 mg/day. Patients meeting the criterion for remission (MADRS total score ≤ 10) at Weeks 10 and 12 were randomized to treatment with placebo or TRINTELLIX (1:1) at the same dose received at the end of the open-label period, and observed for relapse for 24 to 64 weeks during a double-blind treatment period. The primary endpoint was the time to relapse during the first 24 weeks of the double-blind period. Relapse was defined as MADRS total score ≥22 or an unsatisfactory treatment effect (lack of efficacy) as judged by the investigator during the double-blind period.

14.2 Study Results

MDD Short-term Studies

The efficacy of TRINTELLIX 5 mg, 10 mg, 15 mg, and 20 mg once daily was demonstrated in at least one randomized, double-blind, placebo-controlled, 6/8-week, fixed-dose study (including the study in the elderly), as measured by improvement in the primary outcome measure (change from baseline to Week 6/8 in MADRS or HAM-D24 total score). In the non-US studies efficacy was demonstrated with TRINTELLIX 5 mg and 10 mg in two studies and with 15 mg and 20 mg in one study. Efficacy was demonstrated with TRINTELLIX 20 mg in two US studies. In the elderly study, which included US and non-US patients (majority non-US), efficacy was demonstrated with TRINTELLIX 5 mg (Table 8). Less than 100 elderly patients included in the short-term studies in adults received TRINTELLIX at doses above 5 mg/day.

In the studies demonstrating significant improvement on the primary endpoint, TRINTELLIX also showed significant improvement over placebo on key secondary efficacy measures including the proportions of responders (defined as > 50% decrease from baseline in MADRS total score at Week 6/8), proportions of remitters (defined as MADRS total score < 10 at Week 6/8, and in the Clinical Global Impression-Improvement (CGI-I) score at Week 8.

Table 8 - Change from baseline to Week 6/8 in MADRS or HAM-D24 total score in short-term MDD clinical trials

Study number [Primary Measure]	Treatment group	Number of patients	Mean baseline score (SD)	LS Mean change from baseline (SE)	LS Mean difference from placebo (95% CI)	p-value
Study 1*[a,c] [MADRS] Non-US	TRINTELLIX 5 mg	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)	<0.0001
	TRINTELLIX 10 mg	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)	<0.0001
	Placebo	105	33.9 (2.7)	-14.5 (1.0)		
Study 2*[b, c] [MADRS] Non-US	TRINTELLIX 5 mg	155	32.7 (4.8)	-16.5 (0.8)	-1.7 (-3.9, 0.5)	NS
	TRINTELLIX 10 mg	151	31.8 (3.9)	-16.3 (0.8)	-1.5 (-3.7, 0.7)	
	Placebo	145	31.7 (4.3)	-14.8 (0.8)		
Study 3[b, d] [HAM-D24] Non-US	TRINTELLIX 5 mg	139	32.2 (5.0)	-15.4 (0.7)	-4.12 (-6.2, -2.1)	<0.001
	TRINTELLIX 10 mg	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)	<0.001
	Placebo	139	32.7 (4.4)	-11.3 (0.7)		
Study 4*[b, d] [MADRS] Non-US	TRINTELLIX 15 mg	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)	<0.0001
	TRINTELLIX 20 mg	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)	<0.0001
	Placebo	158	31.5 (3.6)	-11.7 (0.8)		
Study 5[b, e] [MADRS] Non-US	TRINTELLIX 5 mg	142	31.6 (3.7)	-14.6 (0.8)	-0.6 (-3.3, 2.0)	NS
	TRINTELLIX 10 mg	147	31.8 (4.0)	-15.7 (0.8)	-1.7 (-4.3, 0.9)	
	TRINTELLIX 20 mg	149	31.7 (3.7)	-15.8 (0.8)	-1.8 (-4.4, 0.8)	
	Placebo	150	31.6 (3.6)	-13.9 (0.8)		
Study 6[a, c] [HAM-D24] US	TRINTELLIX 5 mg	292	32.7 (5.4)	-14.6 (0.7)	-0.74 (-2.5, 1.0)	NS
	Placebo	286	32.1 (5.5)	-13.9 (0.7)		
Study 7*[b, c] [HAM-D24] US	TRINTELLIX 5 mg	153	29.8 (5.6)	-11.1 (0.7)	-0.6 (-2.6, 1.5)	NS
	Placebo	149	29.5 (6.1)	-10.5 (0.8)		
Study 8*[b, d] [MADRS] US	TRINTELLIX 15 mg	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)	NS
	TRINTELLIX 20 mg	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)	0.023
	Placebo	153	31.6 (4.2)	-12.8 (0.8)		
Study 9[b, d] [MADRS] US	TRINTELLIX 10 mg	154	32.3 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)	NS
	TRINTELLIX 20 mg	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)	0.002
	Placebo	155	32.0 (4.0)	-10.8 (0.8)		
Study 10[b, d] [MADRS] US	TRINTELLIX 10 mg	143	34.1 (4.1)	-13.7 (1.1)	-0.79 (-3.7, 2.1)	NS
	TRINTELLIX 15 mg	142	33.7 (4.5)	-13.4 (1.1)	-0.5 (-3.4, 2.5)	
	Placebo	149	33.4 (4.5)	-12.9 (1.0)		
Study 11*[b, c] (elderly) [HAM-D24] Non-US & US	TRINTELLIX 5 mg	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)	0.0011
	Placebo	145	29.4 (5.1)	-10.3 (0.8)		

*Study included active reference treatment

[a] Study duration 6 weeks

[b] Study duration 8 weeks

[c] Primary analysis model: ANCOVA using last observation carried forward, treatment and center as factors and baseline score as covariate

[d] Primary analysis model: MMRM using observed cases, baseline score as covariate
[e] Primary analysis ANCOVA model did not include site as covariate, results presented for post-hoc analysis using ANCOVA model including site as covariate.
NS = non-significant
SD = standard deviation
SE = standard error
CI = confidence interval
LS = least square

MDD Long-term Maintenance of Effect
The maintenance of antidepressant efficacy was demonstrated in a study in which patients in remission (MADRS total score ≤10) for the last 2 weeks of an initial 12-week open-label treatment period with TRINTELLIX (5 or 10 mg/day) were randomized to TRINTELLIX or placebo and observed for relapse during a double-blind period of at least 24 weeks (24-64 weeks). Prior to randomization, the dose of TRINTELLIX was fixed at 5 mg/day or 10 mg/day for at least the last 4 weeks of the open label treatment period. For approximately 70% of randomized patients, the dose of TRINTELLIX at the end of the open-label period and during the double-blind period was 10 mg/day. TRINTELLIX was superior (p=0.004) to placebo on the primary outcome measure, the time to relapse of MDD within the first 24 weeks of the double-blind period, with a hazard ratio of 2.0; that is, the risk of relapse was two times higher in the placebo group than in the TRINTELLIX group.

14.3 Comparative Bioavailability Studies

Not Applicable.

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL TOXICOLOGY

A comprehensive programme of toxicology studies ranging from single-dose studies up to 26- or 52-week repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity studies were conducted for vortioxetine.

Single-Dose/Acute Toxicity
The acute oral single dose toxicity of vortioxetine is relatively low with a maximum tolerated dose (MTD) in mice and rats of 300 and 500 mg/kg, respectively. Clinical signs consisted of marked sensitivity to touch and disturbance, rapid breathing, and brown perinasal staining in rats administered 500 mg/kg. In mice, tremors, sensitivity to touch, eyes partly closed, and hypoactivity were seen after 200 and 300 mg/kg, as well as rapid, noisy and/or labored breathing, incoordination, unsteady gait, leaning, salivation, and hyperactivity after 400 and 500 mg/kg. When administered as two vortioxetine doses given an hour apart (2 x ≥200 mg/kg), clinical signs were more severe, included convulsions, and resulted in death or necessitated euthanasia of moribund rats.

No formal acute toxicity studies were conducted in non-rodents. In a MTD study in dogs given 25 mg/kg/day for 1 week clinical signs of toxicity consisted of salivation, vomiting, abdominal muscle contractions, soft/liquid faeces, subdued behavior, sedation, stiff body and/or legs, pupil dilation, and reduced body weight and food consumption.

Repeat-Dose Toxicity
Administration of vortioxetine in the general toxicity studies in mice, rats and dogs was mainly associated with CNS-related clinical signs. Sporadic salivation generally occurred at all dose levels in rats and at higher dose levels in dogs. Pupil dilatation and impaired pupillary response were the main clinical effects in dogs occurring at all dose levels (≥3.75 mg/kg/day), presumably due to pharmacologic activity. More severe clinical signs in dogs were generally seen at higher dose levels in the 13-week study and included overactivity, unsteady or abnormal gait, prostration, excessive urination, and excitement, as well as convulsions in one dog at each of 10 and 15 mg/kg/day. While no convulsions were seen at the 7.5 mg/kg/day dose level, with a corresponding safety margin of $\underline{\geq}5$ based on systemic (C_{max}) exposure compared to the MRHD of 20 mg/day, one of the convulsions in the dog given 10 mg/kg/day occurred 23 hours post-dose when levels of vortioxetine and its metabolite were likely low.

Target organ toxicity was restricted to kidneys (male rats) and liver (mice and rats) and was mainly attributed to vortioxetine-related crystalline material obstruction of the renal tubules and the bile ducts, respectively, which is considered unlikely to occur in patients at therapeutic doses. The above findings were seen at exposures above those achieved during therapeutic use and considered of low risk to humans. The changes in rat kidney occurred at 80 mg/kg/day (40 mg/kg b.i.d.) and consisted of crystalline material in tubules/papilla/glomeruli, tubular basophilia/regenerative hyperplasia, dilatation of collecting ducts, tubular dilatation, papillary necrosis/foreshortening, hyperplasia of pelvic and/or papillary epithelium, tubular and/or papillary inflammation and interstitial fibrosis or glomerulonephritis, with systemic exposure (AUC0-24h) at the NOEL (40 mg/kg/day) 7 times that at the MRHD.

The NOEL for hepatobiliary toxicity (crystalline material in bile ducts, bile duct hyperplasia, and pericholangitis at 40 and 80 mg/kg/day (20 and 40 mg/kg b.i.d., respectively) in the 26 week rat study was 20 mg/kg/day (10 mg/kg b.i.d.) at which systemic exposure (AUC0-24h) was 1.6 and 2.3 times, in male and female rats, respectively, that at the MRHD. Increased liver weight, hepatocellular hypertrophy, and focal hepatocellular necrosis were also seen, generally at the same dose levels. There were no comparable renal or hepatic effects in dogs at any dose level.

Genotoxicity
Vortioxetine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests that consisted of a bacterial mutagenicity assay, an *in vitro* cytogenetic assay conducted in human peripheral blood lymphocytes, and an *in vivo* male rat bone marrow micronucleus test with plasma concentrations, in terms of C_{max}, of up to 44-fold for vortioxetine compared to the MRHD of 20 mg/day.

Carcinogenicity
CD-1 mice and Wistar rats were given oral doses of vortioxetine up to 50 and 100 mg/kg/day for male and female mice, respectively, and 40 and 80 mg/kg/day (administered as split doses up to 20 and 40 mg/kg b.i.d., respectively) for male and female rats, respectively, for 2 years. These doses in the two species were approximately 12, 24, 20, and 39 times, respectively, the MRHD of 20 mg on a mg/m^2 body surface area basis.

Vortioxetine is not considered to pose a significant risk of carcinogenicity in humans. Small increase in the incidences of hepatocellular adenomas in high dose male mice (50 mg/kg/day) and high dose male (40 mg/kg/day) and female (80 mg/kg/day) rats were considered to be due to chronic hepatotoxicity, which is not apparent in humans. In rats, the incidence of benign polypoid adenomas of the rectum was statistically significantly increased in females at doses 39 times the MRHD, but not at 15 times the MRHD. These were considered related to mucosal

inflammation and hyperplasia in the large intestine and possibly due to exacerbation of an effect of the vehicle (hydroxypropyl- β-cyclodextrin) used for the study. A small statistically significant increase in the incidence of histiocytic sarcomas confined to high dose males (40 mg/kg/day) was considered incidental. A dose-dependent increased incidence of hemangiomas in the mesenteric lymph node of males at 14 and 40 mg/kg/day was also likely incidental, since there was no increase in hemangiosarcomas and vascular tumors were not seen in females or in any other tissue in rats which would generally be considered a more susceptible species for the development vascular tumors.

Reproductive and Developmental Studies
Vortioxetine had no effect on rat fertility, mating performance, reproductive organs, or sperm morphology and motility at dose levels up to 120 mg/kg/day (60 mg/kg b.i.d.) at which plasma vortioxetine concentrations were 24 and 17 times that at the MRHD. Vortioxetine was not teratogenic in rats or rabbits at dose levels up to 160 and 60 mg/kg/day, respectively (80 and 30 mg/kg b.i.d.). However, reproductive toxicity in terms of effects on fetal weight and delayed ossification were seen in the rat at ≥30 mg/kg/day (≥15 mg/kg b.i.d.) with plasma concentrations at the 10 mg/kg/day (5 mg/kg b.i.d.) NOEL corresponding to about 6 times the C_{max} at the MRHD of 20 mg/day. Similar developmental delays were seen in the rabbit at sub-therapeutic exposures.

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 systemic vortioxetine exposures similar to those achieved in humans following administration of vortioxetine 20 mg/day (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Vortioxetine-related material was distributed to the milk of lactating rats (see WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding).

In juvenile toxicity studies in rats, all vortioxetine treatment-related findings were consistent with those noted in adult animals.

Other Toxicity Studies
Immunotoxicity
An immunotoxicity assessment as part of a vortioxetine 13-week toxicity study with 4-week recovery in Han Wistar rats revealed no immunotoxicity reactions based on lymphocyte immunophenotyping and natural killer cell function assays.

17 SUPPORTING PRODUCT MONOGRAPHS

Not Applicable.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTRINTELLIX®
Vortioxetine (as vortioxetine hydrobromide) tablets

Read this carefully before you start taking Trintellix and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Trintellix.

What is Trintellix used for?
Trintellix is used for treatment of depression in adults (18 years of age or older). TRINTELLIX is used to relieve the symptoms of depression which may include:

- feeling sad
- restless
- irritable
- change in weight or appetite
- having a hard time concentrating or sleeping
- feeling tired
- headaches
- unexplained aches and pains.

How does Trintellix work?
Trintellix belongs to a group of medicines called antidepressants. It is thought to work by correcting the imbalance of serotonin in your brain. This may help ease emotional and physical symptoms of depression.

What are the ingredients in Trintellix?
Medicinal ingredients: Vortioxetine hydrobromide
Non-medicinal ingredients: Hydroxypropylcellulose, hypromellose, iron oxide red and/or iron oxide yellow, Macrogol 400, magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate (type A), titanium dioxide (E 171).

Trintellix comes in the following dosage forms:
Tablets: 5 mg (pink), 10 mg (yellow), 15 mg (orange), or 20 mg (red).

Do not use Trintellix if:

- you are allergic to vortioxetine or to any other ingredients in Trintellix.
- you take Monoamine Oxidase Inhibitors (MAOIs).
  - Ask your doctor or pharmacist if you are not sure if you take a MAOI
  - Examples of MAOIs include phenelzine, tranylcypromine, moclobemide, selegiline, rasagiline linezolid which is an antibiotic, methylene blue which is a dye used in certain surgeries
  - If you stopped taking a MAOI within the last 14 days, only start Trintellix if your doctor tells you to.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Trintellix. Talk about any health conditions or problems you may have, including if you:

- have ever had any allergic reaction to medications, food, etc.;
- have any medical conditions, including a history of seizures, liver disease, kidney disease, heart problems;
- are taking or have taken medications (prescription or over-the-counter) and any natural or herbal products within the last 14 days;
- have or previously have had glaucoma or increased pressure in your eyes;
- have a history or family history of mania or bipolar disorder;
- are pregnant or intend to become pregnant, or if you are breast-feeding;
- have a tendency to easily develop bruises or have known bleeding tendencies, or have been told you have low platelets;
- have been told you have a low sodium level in the blood;
- take certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin), acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs);
- are elderly, had a recent bone fracture, were told you have osteoporosis (weak or brittle bones) or have risk factors for osteoporosis;
- have a history of drug abuse

Trintellix is not for use in children and adolescents under 18 years of age.

Other warnings you should know about:

New or Worsened Emotional or Behavioural Problems

Treatment with Trintellix or any type of antidepressant medication is most safe and effective when you and your doctor have good communication about how you are feeling. You may find it helpful to tell a relative or close friend that you are depressed. You might ask them to tell you if they think you are getting worse or if they are worried about changes in your behavior

You may feel worse instead of better when you first start taking drugs like Trintellix or when changing your dose. Your doctor should closely monitor you. You may have:

- new or worsened feelings of restlessness, agitation, anger, aggression, nervousness, short temperament. **If this happens, speak to your doctor.**
- thoughts about suicide, hurting yourself or other people. Thoughts and actions about suicide can occur especially if you have had thoughts of hurting yourself in the past. Suicidal thoughts and actions can occur in any age group but may be more likely if you are 18 to 24 years old. **If this happens, seek immediate medical help.** Do NOT stop taking Trintellix on your own.

Ending treatment**:**

Abruptly ending your treatment of Trintellix may cause you to experience discontinuation symptoms. If your doctor recommends that you stop taking Trintellix, they will gradually lower your dose. This may help manage any symptoms of discontinuation, such as:

- dizziness, headache, runny nose
- increase in dreams/nightmares
- feeling angry suddenly, or mood swings
- muscles feel tight or stiff

Effects on Pregnancy and Newborns

Trintellix should not be used during pregnancy unless your doctor decides the benefit

outweighs the risk to your unborn baby. If you are already taking Trintellix and have just found out that you are pregnant, **you should talk to your doctor immediately**. You should also talk to your doctor if you are planning to become pregnant. It is very important that you **do NOT stop taking Trintellix without first talking to your doctor**.

Some newborn babies experienced problems at birth when pregnant women took drugs similar to Trintellix. This happened especially when the drug was taken in the last three months of pregnancy. Some newborns had:
- required breathing support, tube feeding and a longer stay in the hospital
- difficulty feeding or breathing, fits (seizures), tense or overly relaxed muscles and were jittery and cried constantly.
- vomited, had low blood sugar and body temperature changes
- sleeping difficulties
- a serious condition called Persistent Pulmonary Hypertension in the Newborn (PPHN). This made the babies breathe faster and appear blue.

These symptoms normally resolve over time. However, if your newborn baby has any of these symptoms, please contact your doctor immediately

Risk of breaking bone
Taking Trintellix may increase your risk of breaking a bone if you are elderly or have osteoporosis or have other major risk factors for breaking a bone. You should take extra care to avoid falls especially if you get dizzy or have low blood pressure.

Serotonin Syndrome or Neuroleptic Malignant Syndrome :
Trintellix may cause Serotonin Syndrome or Neuroleptic Malignant Syndrome, rare but potentially life-threatening conditions. There is a potential for serious side effects when Trintellix is taken with other serotonergic and/or antipsychotic drugs. Careful observation by the doctor is recommended if you are taking Trintellix with the following medications:
- Monoamine Oxidase Inhibitors (MAOIs). Examples include linezolid and methylene blue.
- Serotonin Precursors. Examples include L-tryptophan and oxitriptan.
- Other serotonergic drugs. Examples include triptans, lithium, tramadol, most tricyclic antidepressants

Speak to your doctor immediately about ending your treatment with TRINTELLIX if you develop a combination of symptoms, such as:
- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Eye Problems
Trintellix can cause eye problems such as mydriasis. Mydriasis is a condition where your pupils widen in an unusual way. This can cause a build-up of fluid and pressure in your eyes. Tell your doctor right away if you experience visions changes, eye pain, redness in or around the eye.

Driving and Using Machines:
Wait until you know how you feel after you have taken Trintellix for the first time or when changing your dose. Do not drive or use heavy machines until you know how Trintellix affects

you

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Do not use Trintellix if you are taking Monoamine oxidase inhibitors (MAOIs) or have stopped taking an MAOI in the last 14 days. You will need to wait at least 21 days after you stop taking Trintellix before you can start taking an MAOI. Taking MAOIs can increase your chances of having serious side effects. Examples of MAOIs are:

- phenelzine
- tranylcypromine
- moclobemide
- selegiline
- linezolid
- methylene blue

The following may interact with Trintellix:

- other antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) (e.g. fluoxetine, venlafaxine, paroxetine), certain tricyclics (e.g. amitriptyline, desipramine), drugs used to treat schizophrenia (e.g. olanzapine, risperidone), or bipolar depression (e.g. lithium).
- other drugs that affect serotonin, such as lithium, drugs containing tryptophan, St. John's Wort, triptans used to treat migraines
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine.
- certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g. warfarin, dabigatran), acetylsalicylic acid (ASA) and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen).
- certain medicines that can increase the risk of seizures by lowering the seizure threshold (e.g. medicines to treat depression (tricyclics, SSRIs, SNRIs); medicines to treat mental disorders (belonging to the groups called phenothiazines, thioxanthenes, butyrophenones); mefloquin (a medicine to prevent and treat malaria); bupropion (a medicine to treat depression also used to wean from smoking); tramadol (a strong painkiller)
- certain medicines used to treat cough, such as dextromethorphan.
- certain medicines that are strong inhibitors of CYP3A4. Such as itraconazole (antifungal medicine), clarithromycin (antibacterial medicine) and HIV protease inhibitors
- bupropion (an antidepressant and smoking cessation aid), as this may increase your blood levels of Trintellix.
- rifampicin (an antibiotic) as this may lower your blood levels of Trintellix.

Trintellix and urine drug tests: Taking Trintellix may cause false results. Trintellix may cause a urine drug test to show positive results for methadone. If this happens, a more specific test can be performed.

Trintellix and alcohol: Combining Trintellix with alcohol is not advisable.

How to take Trintellix:

- Take one tablet with a glass of water, with or without food.
- Take exactly as the doctor tells you to take it

Usual Adult dose:
18 to 64 years of age: The usual dose is 10 mg once a day. Depending on how you respond, your doctor may:

- Increase your maximum dose to 20 mg once a day
- Decrease your minimum dose to 5 mg once a day

65 years of age and over: The usual starting dose is 5 mg once a day.

Stopping treatment
Continue to take Trintellix for as long as your doctor recommends. Do not suddenly stop taking or change the dose without talking to your doctor first. Suddenly stopping treatment or changing the dose may cause unpleasant side effects.

Overdose:

If you think you have taken too much Trintellix, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Take the Trintellix container with you when you go to the doctor or hospital.

Some of the signs of an overdose could be:

- Dizziness and nausea
- Diarrhea and stomach discomfort
- Itching of whole body
- Sleepiness
- Reddening of skin
- Fits (seizures)
- A rare condition called serotonin syndrome

Missed Dose:
If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using Trintellix?

These are not all the possible side effects you may feel when taking Trintellix. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of Trintellix are:

- Abdominal pain, bloating
- Common cold, Influenza (flu) symptoms
- Nausea, vomiting
- Decreased appetite
- Abnormal dreams and difficulty sleeping
- Dizziness
- Dry Mouth
- Diarrhea, Constipation
- Fatigue, sleepiness

- Sedated (feeling calm)
- Body feels itchy
- Joint and muscle pain
- Increase in sweating
- Cough

Other possible side effects of Trintellix may include:

- Dry eye
- Grinding teeth
- Reddening of skin
- Night sweats
- Weight gain
- Muscle twitching
- Yawning
- Dehydration
- Late menstrual cycle (period) and sensitive breasts

Trintellix may also cause serious side effects including those mentioned above in "**Other warnings you should know about**" and the table below.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Urinary Tract Infection:** Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		**X**	
UNCOMMON **Low platelets:** Bruising or unusual bleeding from the skin or other areas		**X**	
Chest Pain: Discomfort or pressure beneath the breastbone			**X**
RARE **Low sodium level in blood:** Symptoms of tiredness, weakness, confusion combined with achy, stiff, or uncoordinated muscles		**X**	
Hypotension (Low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue		**X**	
Seizures: Loss of consciousness with uncontrollable shaking ('fit')			**X**
Mania:		**X**	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Elevated or irritated mood, decreased need for sleep, racing thoughts			
Serotonin syndrome: A combination of most or all of the following; agitation, tremor, confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat, labile blood pressure, nausea, vomiting, diarrhoea			**X**
Gastrointestinal bleeding: vomiting blood or passing blood in stool			**X**
UNKNOWN FREQUENCY **Allergic reactions (that may be serious):** skin rash, hives, swelling, swelling of the face, lips, tongue or throat, trouble breathing or swallowing, and/or a sudden drop in blood pressure (making you feel dizzy or lightheaded)			**X**
Glaucoma: Increased pressure in your eyes, eye pain, enlarged pupils and blurred vision		**X**	
Pancreatitis (swelling of pancreas)**:** upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			**X**
New or Worsened Emotional or Behavioural Problems: feeling detached, restless, agitated, angry, aggressive, nervous, short tempered		**X**	
Thoughts of death or suicide Thoughts of hurting yourself or other people			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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

Store at room temperature (15^{o} to 30^{o}C), protected from moisture.

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

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.

If you want more information about Trintellix:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.lundbeck.ca, or by calling 1-800-586-2325.

This leaflet was prepared by Lundbeck Canada Inc.

Last Revised March 11, 2021