PRODUCT INFORMATION
BRINTELLIX®

NAME OF THE MEDICINE

Vortioxetine (as hydrobromide)

Chemical Name:

1-{2-[(2,4-dimethylphenyl)sulfanyl]phenyl}piperazine monohydrobromide

CAS Number:

508233-74-7 (vortioxetine base)

960203-27-4 (vortioxetine hydrobromide)

Molecular formula:

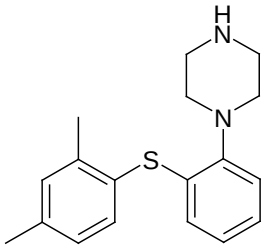
$C_{18}H_{22}N_2S$, HBr

Molecular Mass:

The relative molar mass of vortioxetine base is 298.45

The relative molar mass of vortioxetine hydrobromide is 379.36

Structural Formula:



. HBr

DESCRIPTION

Physicochemical properties:

The drug substance is a white to very slightly beige powder. The molecule is not chiral.

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

Dissociation Constant: pK_a= 9.1 (± 0.1) and 3.0 (± 0.2)

Excipients:

BRINTELLIX film-coated tablets contain mannitol, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycollate type A, magnesium stearate, hypromellose, titanium dioxide, Macrogol 400, iron oxide red (5, 15 and 20 mg tablets) and iron oxide yellow (10 and 15 mg tablets). BRINTELLIX does not contain lactose, gluten, sucrose, tartrazine or any other azo dyes.

PHARMACOLOGY

Mechanism of action:

The mechanism of action of vortioxetine is thought to be related to its multimodal activity,

which is a combination of two pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. *In vitro* studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter (5-HTT).

The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear. However, data from nonclinical serotonergic receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies suggest that the targets interact in a complex fashion, leading to modulation of neurotransmission in several systems, including serotonin, norepinephrine, dopamine, histamine, acetylcholine, gamma-aminobutyric acid (GABA) and glutamate systems within the forebrain. These multimodal pharmacological actions are thought to be responsible for the antidepressant effects of vortioxetine.

Pharmacodynamics:

Vortioxetine shows antidepressant- and anxiolytic-like effects in some animal models (e.g. forced swim, conditioned fear-induced vocalisation, social interaction, marble burying and novelty-induced suppression of feeding tests). It is also effective in the models tested that are predictive of an enhanced effect on cognitive function (learning and memory) (e.g. contextual fear conditioning test and restoration of performance deficits induced by 5-HT depletion in the novel object recognition and Y-maze spontaneous alternation tests). In addition, in a sexual behavioural study in male rats at an oral dose achieving a vortioxetine plasma exposure similar to that at the maximum recommended human dose, vortioxetine did not induce sexual dysfunction.

In humans, two positron emission tomography (PET) studies have been performed using 5-HTT ligands ([^{11}C]-MADAM or [^{11}C]-DASB) to quantify the 5-HT transporter occupancy in the brain across different dose levels. The mean 5-HT transporter occupancy in the specific regions of interest was approximately 50% at 5 mg/day, 65% at 10 mg/day and increased to above 80% at 20 mg/day. Vortioxetine has shown clinical antidepressant effects at 5-HT transporter occupancies as low as 50%.

Pharmacokinetics:

Absorption

The maximal plasma vortioxetine concentration (C_{max}) after multiple oral doses is reached within 7 to 8 hours post-dose (T_{max}). Steady state mean C_{max} values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution

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

Metabolism

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

No inhibitory or inducing effect of vortioxetine was observed *in vitro* for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 nor was an inhibitory effect observed in vitro for CYP2D6 or CYP2El. Vortioxetine is a poor P-gp substrate and inhibitor.

The major metabolite of vortioxetine is (Lu AA34443) pharmacologically inactive.

Excretion

The mean elimination half-life and oral clearance from population PK analysis in healthy volunteers are 66 hours and 33 L/h, respectively.

Approximately 2/3 of the inactive vortioxetine metabolites are excreted in the urine and approximately 1/3 in the faeces. Only negligible amounts of vortioxetine are excreted in the faeces. Steady-state plasma concentrations are achieved in approximately 2 weeks.

Linearity/non-linearity

The pharmacokinetics is linear and time independent in the dose range studied.

Pharmacokinetic/pharmacodynamic relationship(s)

There is a curve-linear concentration-response relationship between the plasma concentrations of vortioxetine after single and multiple doses of 2.5 to 60 mg/day and the occupancy of the 5-HT transporter in the brain, as measured using PET.

Special Populations

Elderly Patients

In elderly healthy subjects (aged ≥65 years; n=20), the exposure to vortioxetine increased up to 27% (C_{max} and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10 mg/day. The recommended starting dose is 5 mg vortioxetine once daily in patients ≥65 years of age (See DOSAGE & ADMINISTRATION).

Renal impairment

Following a single dose of 10 mg vortioxetine, renal impairment estimated using the Cockcroft-Gault formula (mild, moderate, or severe; n=8 per group) caused modest exposure increases (up to 11%), compared to healthy matched controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during the dialysis process (AUC and C_{max} were 13% and 27% lower; n=8) following a single 10 mg dose of vortioxetine. No dose adjustment is needed (See DOSAGE & ADMINISTRATION).

Hepatic impairment

Following a single dose of 10 mg vortioxetine, no impact of mild or moderate hepatic impairment (Child-Pugh Criteria A or B; n=8 per group) was observed on the pharmacokinetics of vortioxetine (changes in AUC less than 10%). No dose adjustment is needed (See DOSAGE & ADMINISTRATION).

CYP2D6 poor metabolisers

The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers. No dose adjustment is needed (See DOSAGE & ADMINISTRATION).

Gender

Systemic exposures are similar between males and females of comparable body size and no dose adjustment is needed.

Race

No dose adjustment on the basis of race or ethnicity is needed based on the population PK study. Race or ethnicity had no apparent effect on the pharmacokinetics of vortioxetine.

CLINICAL STUDIES

Major Depressive Disorder (MDD) Short Term Studies in Adults including Elderly

The efficacy and safety of BRINTELLIX have been studied in a clinical program that included more than 6,700 patients, of whom more than 3,700 were treated with BRINTELLIX in short-term (≤12 weeks) studies in major depressive disorder (MDD). Twelve double-blind, placebo controlled, 6/8-week, fixed-dose studies have been conducted to investigate the short-term efficacy of BRINTELLIX in MDD both in adults and in the elderly. The efficacy of BRINTELLIX was demonstrated across 9 of the 12 studies, as measured by improvement in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item ($HAM\text{-}D_{24}$) total score, and supported by clinical relevance as demonstrated by the proportions of responders and remitters and the improvement in Clinical Global Impression – Global Improvement (CGI-I) score.

In each of the 8 short-term studies in adults that demonstrated statistical superiority the effect seen with BRINTELLIX ranged from 2.4 to 7.2 points difference to placebo in MADRS total score at week 6/8 mixed model repeated measures (MMRM) analysis. The antidepressant effect in the individual studies was supported by the meta-analysis using MMRM of the mean change from baseline in MADRS total score at Week 6/8 in the short-term, placebo-controlled studies in adults. In the meta-analysis, the overall mean difference to placebo across the studies was statistically significant: -2.3 points ($p = 0.007$), -3.6 points ($p < 0.001$), and -4.6 points ($p < 0.001$) for the 5, 10, and 20 mg/day doses, respectively; the 15 mg/day dose did not separate statistically from placebo in the meta-analysis, but the mean difference to placebo was -2.6 points. The efficacy of BRINTELLIX increased with increasing dose.

The efficacy of BRINTELLIX is supported by the pooled responder analysis, in which the proportion of responders ranged from 46% to 49% for vortioxetine versus 34% for placebo ($p < 0.01$; NRI analysis).

Furthermore BRINTELLIX, in the dose range of 5-20 mg/day, demonstrated efficacy on the broad range of depressive symptoms (assessed by improvement in all MADRS single–item scores).

In a 12-week, double-blind, flexible-dose, comparative study in patients with moderate to severe depression who switched antidepressant treatment after an inadequate response to one therapy with SSRI/SNRI for the current episode, BRINTELLIX 10-20 mg/day was statistically significantly better ($p=0.002$) than agomelatine 25-50 mg/day as measured by improvement in the MADRS total score.

In a short-term study, in adults, BRINTELLIX (10 and 20 mg/day) was superior to placebo ($p<0.001$) on the primary outcome measure, a composite cognition score consisting of two neuropsychological tests: a neuropsychological test of executive function, processing speed, and attention, the Digit Symbol Substitution Test (DSST) and a test of learning and memory, the Rey Auditory Verbal Learning Test (RAVLT).

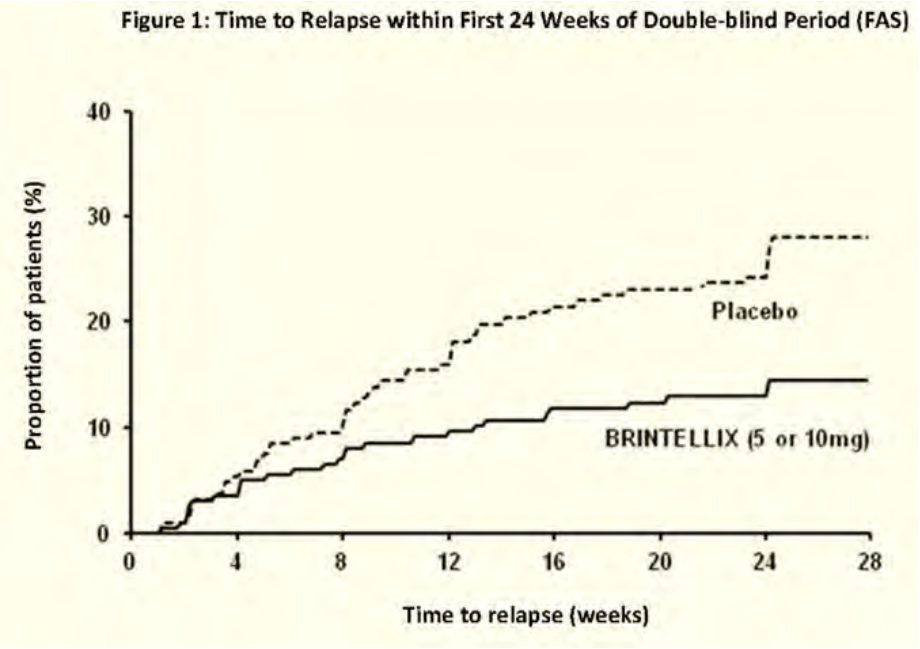
MDD Long term relapse prevention

The maintenance of antidepressant efficacy was demonstrated in a relapse-prevention study. Patients in remission after an initial 12-week open-label treatment period with BRINTELLIX were randomised to BRINTELLIX 5 or 10 mg/day or placebo and observed for relapse during a double-blind period of at least 24 weeks (24 to 64 weeks). A total of 639 patients were treated with open-label BRINTELLIX. Four hundred (62.6%) patients achieved remission and entered the double-blind treatment phase. Remission was defined as MADRS total score ≤10. Relapse was defined as a MADRS total score ≥22 or lack of efficacy, as judged by the investigator.

BRINTELLIX was superior (p=0.004) to placebo on the primary outcome measure, the time to relapse of MDD with a hazard ratio of 2.0; that is, the risk of relapse was two times higher in the placebo group than in the BRINTELLIX group.

Relapse rates during the first 24 weeks of the double-blind period were 13.2% in the combined 5 mg and 10 mg BRINTELLIX groups and 26.0% in the placebo group.

Figure 1: Time to Relapse within First 24 Weeks of Double-blind Period (FAS)



Other Clinical Efficacy Results

Elderly

In the double-blind, placebo-controlled, 8-week, fixed-dose study in elderly (≥ 65 years) depressed patients, BRINTELLIX 5 mg/day was statistically significantly superior to placebo (p=0.001) as measured by improvement in the HAM-D_{24} and MADRS total scores.

Patients with Severe Depression or High Levels of Anxiety Symptoms

In severely depressed patients (baseline MADRS total score ≥30) and in depressed patients with a high level of anxiety symptoms (baseline HAM-A total score ≥20) BRINTELLIX also demonstrated efficacy in the short-term studies in adults (effect size ranged from 2.8 to 7.3 and from 3.6 to 7.3 points difference, respectively, to placebo in MADRS total score at week 6/8 (MMRM analysis)). In the dedicated study in elderly BRINTELLIX was also effective in these patients. The maintenance of antidepressant efficacy was also demonstrated in this patient population in the long-term relapse prevention study.

INDICATIONS

Treatment of major depressive disorder in adults including prevention of relapse.

Vortioxetine is not indicated for paediatric use.

CONTRAINDICATIONS

Hypersensitivity to vortioxetine or any of the tablet excipients (see DESCRIPTION).

Monoamine Oxidase Inhibitors (MAOIs)

BRINTELLIX should not be used in combination with a MAOI, or within at least 14 days of discontinuing treatment with an MAOI. BRINTELLIX should be discontinued for at least 14 days before starting treatment with a MAOI (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Clinical worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16-week), placebo-controlled studies of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 studies), obsessive-compulsive disorder (4 studies), or other psychiatric disorders (4 studies) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder studies, but there were signals of risk arising from studies in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as

well. No suicides occurred in these studies. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for BRINTELLIX should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Serotonin syndrome/Neuroleptic Malignant Syndrome (NMS)

Development of serotonin syndrome /NMS may occur in association with treatment with serotonergic antidepressants, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome/NMS include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with BRINTELLIX should be discontinued if such events occur and supportive symptomatic treatment initiated.

Activation of Mania/Hypomania

As with all drugs effective in the treatment of depression, BRINTELLIX 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. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Seizures

Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, BRINTELLIX should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy (see INTERACTIONS WITH OTHER MEDICINES). Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.

Haemorrhage

As with any antidepressant with serotonergic effect, bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage may occur. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or aspirin) (see INTERACTIONS WITH OTHER MEDICINES), and in patients with known bleeding tendencies.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of antidepressants with serotonergic effect. Caution should be exercised in patients at risk, such as elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

Hepatic Impairment

BRINTELLIX has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients (see DOSAGE AND ADMINISTRATION).

Renal Impairment

Limited data are available for patients with severe renal impairment. Caution should therefore be exercised (see DOSAGE AND ADMINISTRATION).

Electroconvulsive Therapy (ECT)

The safety and efficacy of the concurrent use of BRINTELLIX and ECT have not been studied, and therefore, caution is advisable.

Use in Patients with Concomitant Illness

BRINTELLIX has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease, patients with psychiatric co-morbidities, neurological comorbidities, unstable medical illness or stroke. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Effects on ability to drive and use machines

No significant impairment, relative to placebo, in driving performance, cognitive function or other psychomotor skills, was observed when 21 healthy subjects were administered single and multiple doses of 10 mg/day BRINTELLIX. However, as with any psychoactive drug, patients should exercise caution when driving or operating hazardous machinery especially when starting treatment with BRINTELLIX or when changing the dose.

Effects on fertility

Vortioxetine given prior to and during mating, and in early pregnancy at oral doses achieving exposures 20 times the maximum recommended human dose had no effect on rat fertility, mating performance, or on sperm morphology and motility.

Use in Pregnancy

Category: B3

BRINTELLIX should not be used during pregnancy unless the benefit outweighs the risk. There are no or limited data (fewer than 300 pregnancy outcomes) from the use of vortioxetine in pregnant women.

In studies in which vortioxetine was administered to rats and rabbits during organogenesis, reduced foetal weight and delayed ossification was observed. In rats, these findings were observed at a vortioxetine exposure (plasma AUC) 30 fold or greater than that achieved at the maximum recommended human dose. No increased incidence of foetal malformations was noted. In rabbits, doses associated with delayed ossification, although resulting in vortioxetine exposures (plasma AUC) comparable to that at the maximum recommended human dose, were maternotoxic. In rabbits, an increased incidence of runts was observed at a vortioxetine exposure about 3-fold that at the maximum recommended human dose. A pre- and postnatal study in rats showed reduced pup survival during the lactation period at exposures (plasma AUC) 8 fold or greater than those achieved at the maximum recommended human dose.

The following symptoms may occur in newborns exposed to serotonergic agents in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In a majority of instances, such complications begin immediately or soon (<24 hours) after delivery.

Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Use in lactation

In nonclinical studies vortioxetine-related material was excreted in the milk of lactating rats.

It is expected that vortioxetine will be excreted into human milk. Consequently, breast-feeding is not recommended during treatment.

Paediatric Use

BRINTELLIX is not recommended for the treatment of depression in patients under 18 years of age since safety and efficacy of BRINTELLIX have not been established in this age group. In clinical studies among children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo.

Use in the elderly (≥ 65 years of age)

The recommended starting dose is 5 mg vortioxetine once daily in patients ≥ 65 years of age.

Genotoxicity

Vortioxetine was not genotoxic in a bacterial reverse mutation assay and a chromosome aberration assay in human lymphocytes *in vitro* and an *in vivo* micronucleus test.

Carcinogenicity

Two-year carcinogenicity studies were conducted with vortioxetine in mice and rats at doses which achieved exposures (plasma C_{max}) well in excess of that at the maximum recommended human dose. Although there were some positive findings (increased incidences of hepatocellular adenomas in rats and in male mice, and of haemangiomas in the mesenteric lymph node and of histiocytic sarcomas in male rats, and of polypoid adenomas in the rectum of female rats). None of these findings were considered to pose a risk of carcinogenicity in humans.

Effect on laboratory tests

Drug interaction with laboratory tests has not been established.

INTERACTIONS WITH OTHER MEDICINES

BRINTELLIX is extensively metabolised in the liver primarily through oxidation and subsequent glucuronic acid conjugation. *In vitro* studies indicate that the cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 are involved in the metabolism of vortioxetine (see Pharmacokinetics).

Potential for other medicinal products to affect BRINTELLIX

Irreversible non-selective MAOIs

Due to the risk of serotonin syndrome, BRINTELLIX is contraindicated in any combination with irreversible non-selective MAOIs. For patients changing treatment regimens, BRINTELLIX must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. BRINTELLIX must be discontinued for at least 14 days before starting treatment with an irreversible non-selective MAOI (see CONTRAINDICATIONS).

Reversible, selective MAO-A inhibitor (moclobemide)

The combination of BRINTELLIX with a reversible and selective MAO-A inhibitor (RIMA), such as moclobemide, is not recommended. A latent period of at least 24 hours after the last dose of moclobemide should be introduced before changing treatment to BRINTELLIX.

Moclobemide should not be used for at least 14 days after discontinuation of BRINTELLIX (see CONTRAINDICATIONS).

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with BRINTELLIX. Linezolid should not be used for at least 14 days after discontinuation of BRINTELLIX (see CONTRAINDICATIONS).

Irreversible, selective MAO-B inhibitor (selegiline, rasagiline)

Although a lower risk of serotonin syndrome is expected with selective MAO-B inhibitors as compared with MAO-A inhibitors, the combination of BRINTELLIX with selegiline or rasagiline should be exercised with caution. MAO-B inhibitors should not be used for at least 14 days after discontinuation of BRINTELLIX (see CONTRAINDICATIONS).

Serotonergic medicinal products

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan and other triptans) may lead to serotonin syndrome (see PRECAUTIONS).

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 PRECAUTIONS).

Medicinal products lowering the seizure threshold

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

ECT (electroconvulsive therapy)

There is no clinical experience of concurrent administration of BRINTELLIX and ECT, therefore caution is advisable.

Cytochrome P450 inhibitors

The exposure to vortioxetine increased 2.3-fold for AUC when BRINTELLIX 10 mg/day was co-administered with bupropion (a strong CYP2D6 inhibitor) 150 mg b.i.d. for 14 days in 44 healthy subjects. The co-administration resulted in a higher incidence of adverse events when bupropion was added to BRINTELLIX than when BRINTELLIX was added to bupropion. Depending on individual patient response, a lower dose of BRINTELLIX may be considered if strong CYP2D6 inhibitors (e.g. bupropion) are added to BRINTELLIX treatment (see DOSAGE AND ADMINISTRATION).

When BRINTELLIX was co-administered following 6 days of ketoconazole 400 mg/day (a CYP3A4/5 and P-glycoprotein inhibitor) in 17 healthy subjects, a 1.3-fold increase in vortioxetine AUC was observed. No dose adjustment is needed.

When BRINTELLIX was co-administered following 6 days of fluconazole 200 mg/day (a CYP2C9, CYP2C19 and CYP3A4/5 inhibitor) in 16 healthy subjects, a 1.5-fold increase in AUC was observed. No dose adjustment is needed.

Cytochrome P450 inducers

When a single dose of 20 mg BRINTELLIX was co-administered following 10 days of rifampicin 600 mg/day (a broad inducer of CYP isozymes) in 14 healthy subjects, a 72%

decrease in AUC of BRINTELLIX was observed. Depending on individual patient response, a dose adjustment may be considered (see DOSAGE AND ADMINISTRATION).

Potential for BRINTELLIX to affect other medicinal products

Anticoagulants and antiplatelet agents

No significant effects, relative to placebo, were observed in INR, prothrombin or plasma R-/S-warfarin values following co-administration of 10 mg/day vortioxetine for 14 days with stable doses of warfarin in 52 healthy subjects. Also, no significant inhibitory effect, relative to placebo, on platelet aggregation was observed when aspirin 150 mg/day was co-administered following 14 days of BRINTELLIX 10 mg/day administration in 28 healthy subjects. However, as for other serotonergic agents, caution should be exercised when vortioxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see PRECAUTIONS).

Lithium, tryptophan

No clinically relevant effect was observed during steady-state lithium exposure following co-administration with BRINTELLIX 10 mg/day for 14 days in 16 healthy subjects. However, there have been reports of enhanced effects when antidepressants with serotonergic effect have been given together with lithium or tryptophan, therefore concomitant use of vortioxetine with these medicinal products should be undertaken with caution.

Alcohol

Overall no impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for BRINTELLIX single doses of 20 and 40 mg following co-administration with a single dose of ethanol 0.6 g/kg in 55 healthy subjects.

Diazepam

No significant impairment, relative to placebo, in cognitive function using a battery of neuropsychological tests was observed for vortioxetine following co-administration of BRINTELLIX 10 mg/day with a single 10 mg dose of diazepam in 32 healthy subjects.

Oral contraceptives

No significant effects, relative to placebo, were observed in the levels of sex hormones following co-administration of BRINTELLIX 10 mg/day with a combined oral contraceptive (ethinyl estradiol 30 µg/ levonorgestrel 150 µg) in 25 healthy women for 21 days.

Cytochrome P450 substrates

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

No inhibitory effect of vortioxetine (10 mg/day for 14 days) was observed in healthy subjects for the cytochrome P450 isozymes CYP2C19 (omeprazole, diazepam), CYP2C9 (warfarin), CYP3A4/5 (ethinyl estradiol), or CYP2B6 (bupropion). In a drug-drug interaction study in healthy subjects, no inhibitory effect of vortioxetine 10 mg/day for 14 days was observed for CYP2C9 (tolbutamide), CYP1A2 (caffeine), or CYP3A4/5 (midazolam), while CYP2D6 (dextromethorphan) was affected, the decrease in dextromethorphan levels was not considered clinically meaningful.

ADVERSE EFFECTS

Adverse events information for BRINTELLIX was collected in patients with MDD in a

clinical programme that included more than 6,700 patients, of whom 3,460 were treated with BRINTELLIX (5 to 20 mg/day) in short-term placebo-controlled (up to 8 weeks) studies.

During clinical studies, 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 females and 33% were males.

Major Depressive Disorder (MDD) Short Term Studies in Adults and Elderly

Adverse events that occurred in BRINTELLIX treated patients in the course of the MDD short-term, placebo-controlled studies with an incidence ≥10% were headache and nausea. The incidence of headache was 13.2% with BRINTELLIX and 12.9% with placebo, which suggests that this is a non-specific symptom related to the underlying condition or treatment administration. The incidence of nausea was higher with BRINTELLIX (24.1%) compared to the lower rates of nausea in the placebo group (8.1%). The majority of cases of nausea in the MDD Short-Term studies were transient and mild to moderate and did not generally lead to cessation of therapy. Gastrointestinal adverse reactions, such as nausea, occurred more frequently in women than men.

In the MDD short-term studies, discontinuation due to adverse events was more common with BRINTELLIX (6.0%) compared with placebo (4.0%). Nausea was the most common reason for patients discontinuing due to adverse events.

Table 1 enumerates the incidence of treatment emergent adverse events that occurred in the short term placebo-controlled studies. Events included are those occurring in 1% or more of patients treated with BRINTELLIX (5 to 20 mg/day), and for which the incidence in patients treated with vortioxetine was greater than the incidence in placebo-treated patients.

TABLE 1
INCIDENCE OF COMMON ADVERSE EVENTS
FOR MAJOR DEPRESSIVE DISORDER, POOL OF 12 SHORT-TERM STUDIES

Body System/Adverse Event	**Percentage of Patients Reporting**				
	BRINTELLIX **5 mg/day (n=1157)**	BRINTELLIX **10 mg/day (n=1042)**	BRINTELLIX **15 mg/day (n=449)**	BRINTELLIX **20 mg/day (n=812)**	**Placebo (n=1968)**
Gastrointestinal Disorders					
Nausea	20.5*	22.6*	31.2*	27.2*	8.1
Diarrhoea	6.6	5.4	9.4*	5.5	5.5
Dry mouth	6.4	5.5	6.0	6.5	5.6
Constipation	3.4	3.6	5.6*	4.4*	2.9
Vomiting	2.7*	3.6*	6.5*	4.4*	1.1
Dyspepsia	1.8	1.7	2.4	2.1	1.9
Flatulence	1.0	1.9	2.0	0.9	1.2
Abdominal discomfort	1.4	0.6	2.0	1.6	1.1
General Disorders and Administration Site Conditions					
Fatigue	3.1	2.8	3.6	2.6	2.7
Infections and Infestations					
Nasopharyngitis	5.3	4.0*	3.6	4.9	3.9
Influenza	1.5	1.6*	0.9	0.4	1.1
Injury, poisoning and procedural complications					
Accidental overdose	1.3	1.2	1.3	0.9	1.0
Metabolism and Nutrition Disorders					
Decreased appetite	2.1*	0.7	0.7	1.6	1.0
Musculoskeletal and Connective Tissue Disorders					
Back Pain	2.2	2.1	1.8	1.1	1.8
Arthralgia	0.9	0.9	1.8	1.1	0.9
Nervous System					
Headache	13.7	12.7	14.7	12.4	12.9
Dizziness	5.5	5.2	7.1	6.3	5.3
Somnolence	3.3	2.9	2.7	3.3	2.3
Sedation	1.2	0.5	1.3	1.5*	0.6
Psychiatric Disorders					
Insomnia	3.1	2.6	1.8	2.7	2.5
Skin and Subcutaneous Tissue Disorders					
Hyperhidrosis	2.3	2.3	1.8	0.7	1.7
Pruritus generalised	0.4	1.3*	1.6*	1.8*	0.4

* Adverse events for which the difference to placebo is statistically significant ($p<0.05$)

Male and Female Sexual Dysfunction

Difficulties 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.

In the MDD 6 to 8 week placebo-controlled clinical studies with BRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the incidence was 1.6% for BRINTELLIX (5-20 mg; n=3460) compared to 0.9% for placebo (n=1968).

Because voluntarily reported adverse sexual reactions are known 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 seven placebo-controlled trials. 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.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 2* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with BRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

TABLE 2
ASEX INCIDENCE OF TREATMENT EMERGENT SEXUAL DYSFUNCTION IN A POOL OF 7 PLACEBO-CONTROLLED CLINICAL STUDIES*

	BRINTELLIX **5 mg/day** N=65:67†	BRINTELLIX **10 mg/day** N=94:86†	BRINTELLIX **15 mg/day** N=57:67†	BRINTELLIX **20 mg/day** N=67:59†	**Placebo (n=1968)** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

*Incidence based on number of subjects with sexual dysfunction during the study / number of subjects without sexual dysfunction at baseline. 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.
†Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline.

Insomnia

Although insomnia is common in patients with depression, either as part of the disease or as an adverse effect of antidepressants, for vortioxetine, the reporting of adverse events related to insomnia and poor quality sleep is low and similar to placebo. Side-effects related to insomnia or poor quality sleep may affect treatment adherence.

Table 3 shows the percentage of reported adverse reactions related to insomnia or poor sleep quality in the short-term studies in patients with MDD.

TABLE 3
INCIDENCE OF INSOMNIA RELATED SIDE EFFECTS IN A POOL OF 12 PLACEBO-CONTROLLED CLINICAL STUDIES FOR MAJOR DEPRESSIVE DISORDER

Adverse Event	Percentage of Patients Reporting	
	BRINTELLIX (5-20 mg) (n =3460)	Placebo (n = 1968)
Insomnia	2.7	2.5
Initial insomnia	0.5	0.3
Sleep disorder	0.2	0.4
Middle insomnia	0.3	0.3
Poor quality sleep	<0.1	0.3
Dyssomnia	<0.1	0.1
Terminal insomnia	<0.1	0.0

Discontinuation symptoms

BRINTELLIX was not associated with an increase in signs or symptoms consistent with withdrawal effects.

Weight

BRINTELLIX was not associated with weight gain (<1 kg) in either short or long-term clinical studies.

Cardiovascular

BRINTELLIX was not associated with clinically significant effects on vital signs or the ECG. In a randomised, placebo- and positive-controlled, parallel group, thorough QTc study in 340 healthy subjects, treatment with BRINTELLIX 10 or 40 mg/day for 14 days did not prolong the QTc interval.

Adverse Events during Treatment up to 64 weeks

The adverse event profile of BRINTELLIX in a longer term study in patients with MDD consisting of a 24-64 week placebo-controlled relapse observation phase in remitters after a preceding 12-week acute treatment phase was similar to that observed in short-term studies.

During long-term, double-blind treatment the overall incidence of Treatment-Emergent Adverse Events (TEAEs) was 62% for BRINTELLIX and 64% for placebo. Table 4 enumerates the incidence of TEAEs that occurred in 204 depressed patients who received BRINTELLIX at 5 or 10 mg/day for 24 to 64 weeks. Events included are those occurring in 2% or more of patients treated with BRINTELLIX, and for which the incidence in patients treated with BRINTELLIX was greater than the incidence in placebo-treated patients.

TABLE 4

INCIDENCE OF ADVERSE EVENTS ≥2% FOR DOUBLE-BLIND PERIOD OF MDD RELAPSE PREVENTION STUDY

Adverse Event	Percentage of Patients Reporting	
	BRINTELLIX **5 or 10 mg (n =204)**	**Placebo (n = 192)**
Nausea	8.8	3.1
Influenza	6.9	5.2
Gastroenteritis	5.4	3.1
Abdominal pain upper	4.9	1.0
Insomnia	2.5	1.6
Dry mouth	2.0	0.0
Back pain	2.0	0.5
Asthenia	2.0	0.5

Less Common Clinical Study Adverse Drug Reactions

The events listed below present treatment emergent adverse events occurring in less than 1% of the patients treated with BRINTELLIX (5 to 20 mg/day) in 12 short-term placebo-controlled studies in depressed patients (n=3460). 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 events are categorised by body system according to the following definitions: Uncommon adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in less than 1/1000 patients.

Ear and Labyrinth Disorders

Uncommon: Vertigo

Eye Disorders

Uncommon: Dry eye

Gastrointestinal Disorders

Uncommon: Abdominal distension, gastritis, epigastric discomfort, salivary hypersecretion

General Disorders and Administration Site Conditions

Uncommon: Chest discomfort, malaise

Investigations

Uncommon: Weight increased, electrocardiogram QT prolonged, heart rate increased, low density lipoprotein increased, blood cholesterol increased, blood triglycerides increased

Nervous System

Uncommon: Dysgeusia, lethargy, tremor, myoclonus, formication

Psychiatric Disorders

Uncommon: Tension, bruxism, abnormal dreams, restlessness, derealisation

Renal and Urinary Disorders

Uncommon: Micturition urgency, nocturia

Skin and Subcutaneous Tissue Disorders

Uncommon: Pruritus, night sweats, rash

Vascular Disorders

Uncommon: Flushing, hypotension

DOSAGE AND ADMINISTRATION

The starting and recommended dose of BRINTELLIX in adults less than 65 years of age is 10 mg once daily, taken with or without food. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily or reduced to a minimum of 5 mg daily.

An antidepressant effect of BRINTELLIX based on the primary efficacy measure was generally observed starting at week 2. If the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

Physicians should periodically re-evaluate the usefulness of the drug for individual patients.

Treatment discontinuation

Patients being treated with BRINTELLIX can abruptly stop taking BRINTELLIX without the need for a gradual reduction in dose.

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.

Special Populations

Paediatric population

The safety and efficacy of BRINTELLIX in children and adolescents aged less than 18 years have not been established. No data are available (see PRECAUTIONS). BRINTELLIX is not indicated for use in patients below the age of 18.

Elderly patients

The recommended starting dose is 5 mg vortioxetine once daily and should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily.

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 Pharmacokinetics).

Patients with hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment.

BRINTELLIX has not been studied in patients with severe hepatic impairment and caution should be exercised when prescribing to these patients (see Pharmacokinetics).

Cytochrome P450 inhibitors

Depending on individual patient response, a lower dose of BRINTELLIX may be considered if strong CYP2D6 inhibitors (e.g. bupropion) are added to BRINTELLIX treatment.

Cytochrome P450 inducers

Depending on individual patient response, a dose adjustment of BRINTELLIX may be considered if a broad cytochrome P450 inducer (e.g. rifampicin) is added to BRINTELLIX treatment.

OVERDOSAGE

There is limited experience with BRINTELLIX in overdose. In clinical studies no patients ingested more than 75 mg vortioxetine on a single occasion. The clinical studies included subjects who were administered 40 to 75 mg. Ingestion of vortioxetine in this dose range caused an aggravation of the following adverse events: nausea, postural dizziness, diarrhoea, abdominal discomfort, generalized pruritus, somnolence and flushing. Management of overdose should consist of treatment of clinical symptoms and relevant monitoring. Medical follow-up in a specialised environment is recommended.

For information on the management of overdose, contact the Poison Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Each BRINTELLIX 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.

Blister packs: Transparent; PVC/PVdC/aluminium blister.

Pack sizes of 7 (10 mg only) and 28 film-coated tablets (all strengths).

Storage conditions

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

Lundbeck Australia Pty Ltd

Ground Floor

1 Innovation Rd

North Ryde NSW 2113

Ph: +61 2 8669 1000

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

31 March 2014