

Brintellix® (vortioxetine) FACT SHEET

Brintellix Approval and Dosing

- Brintellix (pronounced “Brin-téll-ix”) (vortioxetine) was approved by the U.S. Food and Drug Administration (FDA) on September 30, 2013 for the treatment of adults with major depressive disorder (MDD), commonly referred to as clinical depression.
- Brintellix is a once-daily oral medication approved at a broad dose range of 5-20 mg, with a recommended starting dose at 10 mg/day (without regard to meals) increased to 20 mg/day (as tolerated). Higher doses demonstrated better treatment effects in clinical trials conducted in the United States (U.S.). A decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses.

Brintellix®
vortioxetine
5mg•10mg•20mg tablets

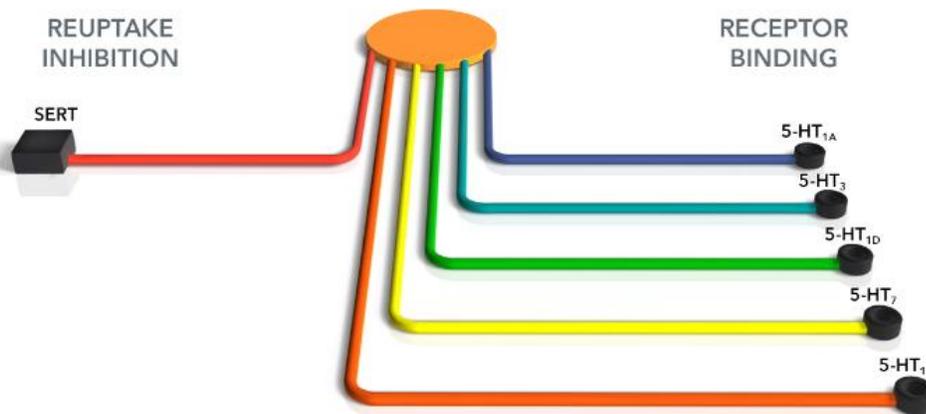


Clinical Pharmacology

Mechanism of Action

- The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT₃ receptor antagonism and 5-HT_{1A} receptor agonism. The contribution of these activities to vortioxetine’s antidepressant effect has not been established.

Pharmacodynamics



The clinical relevance of the pharmacologic activity is unknown.

In vitro studies also indicate that vortioxetine is a 5-HT_{1D} and 5-HT₇ receptor antagonist, and a 5-HT_{1B} receptor partial agonist. The clinical relevance of this is unknown.

Clinical Development Program Overview

- The FDA approval of Brintellix was supported by a comprehensive clinical development program.
 - FDA approval based on seven positive pivotal trials, including six, 6-8 week short-term studies and one 24-64 week long-term maintenance study.
 - Safety was evaluated in more than 4,700 MDD patients aged 18 to 88 years.
 - Efficacy was evaluated in more than 2,700 MDD patients aged 18 to 88 years.



Pivotal Trials

- Improvement in the overall symptoms of depression was assessed across six, 6-8 week randomized, double-blind, placebo-controlled, fixed-dosed studies (including one study in the elderly).
 - The primary efficacy measure was the mean change from baseline to endpoint in the Hamilton Depression Scale (HAMD-24) total score in two short-term studies, including the elderly study, and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in the other studies.
- In the randomized, double-blind, placebo-controlled, maintenance study, time to recurrence of depressive episodes (defined as a MADRS total score > 22 or as judged by the investigator) was evaluated in MDD patients in remission following treatment with open-label Brintellix for 12 weeks.

Most Common Adverse Events and Other Information

- The most commonly observed adverse events in MDD patients treated with Brintellix in 6-8 week placebo-controlled studies (incidence ≥5 percent and at least twice the rate of placebo) were nausea, constipation and vomiting.
- Overall, 5 to 8 percent of the patients who received Brintellix 5 to 20 mg/day in short-term trials discontinued treatment due to an adverse reaction, the most common being nausea, compared with 4 percent of placebo-treated patients in these studies.
- In the 6-8 week placebo-controlled clinical studies, and the 6-month double-blind, placebo-controlled phase of the long-term study in patients who had responded to Brintellix during the initial 12-week, open-label phase, Brintellix had no significant effects on body weight as measured by the mean change from baseline.
- Brintellix has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.
- Brintellix and other antidepressants may cause serious side effects. See [Important Safety Information](#) below.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

BRINTELLIX has not been evaluated for use in pediatric patients.

CONTRAINDICATIONS

Hypersensitivity: Hypersensitivity to vortioxetine or any components of the BRINTELLIX formulation. Angioedema has been reported in patients treated with BRINTELLIX.



Monoamine Oxidase Inhibitors (MAOIs): Due to an increased risk of serotonin syndrome, do not use MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX. Do not use BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. Do not start BRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times 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 who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania), especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients daily.**

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants (SNRIs, SSRIs, and others), including BRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If such symptoms occur, discontinue BRINTELLIX and any concomitant serotonergic agents, and initiate supportive symptomatic treatment. If concomitant use of BRINTELLIX is clinically warranted, patients should be made aware of and monitored for potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Abnormal Bleeding: Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania: Activation of mania/hypomania can occur with antidepressant treatment. Prior to initiating treatment with an antidepressant, screen patients for bipolar disorder. As with all antidepressants, use BRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Hyponatremia: Hyponatremia has occurred as a result of serotonergic drugs and in many cases, appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. More severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinue BRINTELLIX in patients with symptomatic hyponatremia and initiate appropriate medical intervention.

Adverse Reactions: The most commonly observed adverse reactions for BRINTELLIX in 6- to 8-week placebo-controlled studies (incidence $\geq 5\%$ and at least twice the rate of placebo) were by dose (5 mg, 10 mg, 15 mg, 20 mg) vs placebo: nausea (21%, 26%, 32%, 32% vs 9%), constipation (3%, 5%, 6%, 6% vs 3%), and vomiting (3%, 5%, 6%, 6% vs 1%).

Drug Interactions: Concomitant administration of BRINTELLIX and strong CYP2D6 inhibitors or strong CYP inducers may require a dose adjustment of BRINTELLIX.



INDICATION

BRINTELLIX is indicated for the treatment of major depressive disorder in adults.

Please see full [Prescribing Information](#) and [Medication Guide](#) for BRINTELLIX.

About Takeda and Lundbeck Alliance

In September 2007, Lundbeck and Takeda Pharmaceutical Company Limited formed a strategic alliance for the exclusive co-development and co-commercialization in the U.S. and Japan of several compounds in Lundbeck's pipeline for the treatment of mood and anxiety disorders. The companies plan to co-promote Brintellix in the U.S. for the commercial launch of the product. The Lundbeck–Takeda alliance in the U.S. will benefit from the synergy of Lundbeck's longstanding expertise and knowledge of psychiatry and Takeda's understanding and established presence in the very important primary care environment.

About MDD

Major depressive disorder is a complex mental health illness that affects approximately 14 million people, in any given year, as estimated by the 2001-2002 National Comorbidity Survey-Replication. Also known as clinical depression, MDD may trigger emotional, cognitive and physical symptoms, which includes depressed mood, loss of interest or pleasure, significant weight loss or gain or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, or indecisiveness, and recurrent suicidal ideation. It can be a serious condition in which symptoms are persistent and periods of wellness alternate with recurrences of illness.

For more information about Brintellix, please visit www.Brintellix.com.