

Brand Name: Brintellix

Generic Name: Vortioxetine

Manufacturer⁵: Takeda Pharmaceuticals, Inc.

Drug Class^{2,5}: Antidepressant, Piperazine

Uses:

Labeled Uses^{1,2,3,4,5}: Major depressive disorder

Unlabeled Uses^{6,7}: None listed

Mechanism of Action:^{1,2,3,4,5}

The exact mechanism of vortioxetine is unknown. However, potent inhibition of the serotonin transporter is the main mechanism. It acts as a serotonin receptor antagonist at 5-HT₃, 5-HT_{1D}, and 5-HT₇, a partial agonist at 5-HT_{1B}, and an agonist at the 5-HT_{1A} receptor.

Pharmacokinetics^{1,2,3,4,5}:

Absorption:

| | |
|------------------|------------|
| T _{max} | 7-11 hours |
| V _d | 2,400 L |
| t _{1/2} | 57 hours |
| Protein binding | 98-99% |
| Bioavailability | 75% |

Metabolism: Vortioxetine is extensively metabolized in the liver, primarily CYP2D6 (major), CYP3A4 (major), CYP2C19 (minor), CYP2C9 (minor), CYP2A6 (minor), CYP2C8 (minor), and CYP2B6 (minor). It is further metabolized by glucuronic acid conjugation.

Elimination: Vortioxetine is primarily excreted by the kidneys. They excrete 59% of the drug as metabolites. Additionally, approximately 29% of the drug is excreted in the feces as metabolites.

Efficacy^{7,8,9}:

Henigsberg N, Mahableshawarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry 2012; 73(7): 953-9.

Study Design: Randomized, multicenter, double-blind, placebo-controlled, parallel-group design study.

Description of Study: *Methods:* A total of 560 subjects were randomized to receive vortioxetine 5 mg, 10 mg, or placebo for 8 weeks. The subjects were required to have a Montgomery-Asberg Depression Rating Scale score greater than or equal to 26 and have a diagnosis of major depressive disorder. Subjects were excluded if they scored greater or equal to 5 on the suicidal thoughts sections of the MARDS or had made a suicide attempt in the last 6 months. Additionally subjects were excluded if they failed 2 previous antidepressant treatments, had a psychiatric disorder history other than MDD, had a neurologic or substance abuse disorder, current clinically significant medical illness, or significant abnormalities in vital signs or laboratory values. The primary endpoint was reduction in the 24-Item Hamilton Depression rating scale. Secondary outcome measures included the Sheehan Disability Scale, Clinical Global Impressions-Global Improvement scale, MARDS total score, and HDRS-24 total score in subjects with baseline Hamilton Anxiety Rating Scale scores greater than or equal to 20. Adverse events were also monitored throughout the study.

Results: The primary endpoint showed that vortioxetine was effective at significantly reducing HDRS-24 total score at week 8 in the vortioxetine 10 mg treatment group compared to placebo ($P < 0.001$). Secondary endpoints showed statistically significant improvements in HDRS-24 total score, response and remission rates, CGI-I score, MARDS total score, and HDRS-24 total score in subjects with baseline HDRS score greater than or equal to 20 at week 8 in all treatment groups versus placebo. No significant differences were seen in SDS scores. Adverse events were reported from 45.1% of patients with 56.4% reported in the 5 mg vortioxetine treatment group, 41.7% in the 10 mg treatment group, and 42.9% in the placebo group. The majority of adverse effects were mild to moderate and the most frequently reported adverse effects were nausea, headache and dizziness.

Limitations: This study was funded by Takeda Pharmaceutical Company, the manufacturer of vortioxetine and several of the authors are employees of Takeda. The ability of this trial to extrapolate results is limited by the exclusion of subjects with significant psychiatric, substance abuse, or medical disorders, which are common comorbid conditions in patients with MDD. Additionally, the placebo response rate was lower than some other studies. This placebo fluctuation could be responsible for increased response seen in the active treatment groups.

Conclusion: Based on this study vortioxetine 10 mg is possibly effective in the treatment of patients with MDD. Additionally, vortioxetine appears to be a relatively safe medication with few major side effects. Further study is needed to assess patients' response in the United States and to duplicate results to account for placebo response fluctuations.

Bidzan L, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) in generalized anxiety disorder: Results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial, *European Neuropsychopharmacology* 2012; 22(12): 847-857.

Study Design: Multicenter, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: Methods: The study included a total of 301 subjects that were randomized to vortioxetine 5 mg (n=150) or placebo (n=151) for 8 weeks. Inclusion criteria included men and non-pregnant women greater than or equal to 18 years of age. Patients were eligible if they had a primary diagnosis of Generalized Anxiety Disorder (GAD) as well as a HAM-A total score greater than or equal to 20 at screening and baseline. Additionally, patients had to have a MARDS total score less than or equal to 16 at screening and baseline. Patients were excluded if they had a current psychiatric disorder other than GAD, personal history of manic or hypomanic episodes, schizophrenia, neurological disorder, neurodegenerative disorder, or any Axis II disorder that might compromise the study. Patients were also excluded if they had a substance use disorder with the exceptions of nicotine and caffeine, if they posed a significant risk of suicide, or had previously failed to respond to adequate treatment with an SSRI or SNRI (at the investigators discretion). The primary outcome measure was reduction in HAM-A total scores from baseline. Secondary outcome measures were HAD anxiety sub-score, CGI-I, SDS total score, and HAM-A response rates.

Results: The primary endpoint showed that vortioxetine provided significant improvement in the change from baseline in HAM-A total score compared to placebo ($p < 0.001$). Vortioxetine also showed statistically significant improvements in the secondary endpoints CGI-I, SDS total score, HAM-A response rates, HAM-A total score in patients with baseline HAM-A total score greater than or equal to 25, and SF-36 social functioning sub score. The SDS score difference did not reach statistical significance. A subgroup analysis was also performed by age for patients less than or equal to 55 and patients greater than 55, HAM-A total score less than 25 and greater than or equal to 25, and gender. This result showed significant improvement in the primary endpoint with all sub groups except those greater than the age of 55. The adverse events occurring in greater than or equal to 5% were nausea, headache, and dizziness. No serious adverse events related to treatment were seen in any group.

Limitations: This study had several limitations. This study was funded by Takeda and several of the authors are employees of this company. An active control was not used in this study. The entire population of subjects in this study were causation. Patients were excluded if they had any comorbid medical or psychiatric conditions, substance abuse histories, or receiving concurrent treatment. These patient population factors could have contributed to an inability to extrapolate results to the typical patient with GAD. Finally, Samples were not collected for pharmacokinetic analysis. This diminishes the ability to determine both adherence and how adverse events relate to serum concentrations.

Conclusion: Based on this study vortioxetine is possibly effective in the treatment of GAD. It is also a relatively safe medication to use in these patients. However, due to the design limitations, results cannot be extrapolated to patients in the United States. Further research is needed to confirm these results and provide data for a patient population included within the United States.

Rothschild AJ, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: Results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States, European Neuropsychopharmacology 2012; 22(12): 858-866.Study

Design: Double blind, multicenter, randomized, placebo-controlled parallel study in the United States

Description of Study: Methods: This study included 304 patients that were randomized to receive either vortioxetine 5 mg or placebo. Men and non-pregnant women were included if they had a primary diagnosis of GAD according to DSM-VI-TR classification, HAM-A total score greater than or equal to 20, a score greater than or equal to 2 on the anxious mood or tension sections of the HAM-A, and a MARDS total score of less than or equal to 16 at screening and at baseline. Exclusion criteria included, patients with a psychiatric disorder other than GAD, and personal history of a neurological or neurodegenerative disorder. Additionally, patients were excluded if they posed a significant risk of suicide defined by a score of greater than 5 on the suicidal thoughts section of the MARDS or if they had made an attempt at suicide in the last 6 months. Finally, patients were excluded if they previously failed to respond to adequate therapy with an SSRI or SNRI. The primary endpoint was the change from baseline in HAM-A total score at 8 weeks of treatment. Secondary endpoints included change from baseline in HAD anxiety and depression sub scales, SF-36 domain sub scores, CGI-S, CGI-I, and HAM-A response. Safety was assessed with spontaneous adverse event reporting, physical examinations, vital signs, laboratory tests, ECGs, and the administration of the C-SSRS.

Results: The results did not show statistically significant differences in any of the primary or secondary endpoints. The majority of adverse events seen were mild to moderate and nausea, headache, dizziness, and dry mouth were the most frequently occurring events.

Limitations: The study was funded by Takeda and several of the authors are employees of this company. The lack of an active control made it impossible to discriminate between a lack of efficacy and a flawed trial. The trial recruited patients through advertisements rather than physician referrals. This can select a different patient population than what would normally be encountered. Additionally, the baseline scores in the sample were inflated compared to the normal values seen. This may represent the study's intentional or unintentional bias to include patients in the study. Finally multiple raters were used in a single subject. This introduces the possibility of inconsistency and rater bias.

Conclusion: This study suggests vortioxetine is relatively safe, but ineffective in the treatment of GAD. This contradicts a similar trial described above that was performed outside the United States. Further research using an active control could possibly separate a flawed design from a true lack of efficacy. However, regardless of the reason for failure, vortioxetine cannot be recommended for the treatment of GAD at this time.

Contraindications^{1,2,3,4,5}:

Familial Short QT syndrome: Vortioxetine is contraindicated with MAOIs. It should not be started within 14 days of discontinuing an MAOI. Additionally an MAOI should not be started within 21 days of discontinuing vortioxetine. It is also contraindicated in all patients with a hypersensitivity to any component of the product's formulation.

Precautions^{1,2,3,4,5}:

Suicidal ideation, unusual changes in behavior, or worsening depression: There is increased risk in children, adolescents, and young adults. All patients should be monitored with special attention given to the first few months of therapy and following dosage changes. Discontinuation may be necessary if the above listed precautions are seen.

Personal history or family history of bipolar disorder: There is an increased risk provoking a mixed/manic episode when using only anti depressant treatment.

Bleeding events: Patients can be at an increased risk of bleeding when used concomitantly with other drugs that affect coagulation or bleeding.

Hepatic impairment: use is not recommended in patients with severe hepatic impairment

Hyponatremia or SIADH: Risk is increased in elderly patients or patients with volume depletion. Concurrent diuretic medications can also contribute to risk. Therapy should be discontinued with symptomatic hyponatremia.

Personal or family history of mania or hypomania: Patients are at risk of an activation of mania or hypomania.

Serotonin syndrome: This condition has been reported with serotonergic antidepressants. Concomitant use other medications affecting serotonin can increase the risk. These agents include triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, Saint John's wort. Additionally, drugs that impair the breakdown of serotonin can contribute to risk. These agents include MAOIs, methylene blue IV and linezolid. Patients should be monitored when therapy is started and when dosages are modified. Discontinue therapy if serotonin syndrome is suspected.

Adverse Effects^{2,3,4,5}:

Dermatologic Effects:

Pruritus (1% to 3%)

Gastrointestinal

Constipation (3% to 6%)

Diarrhea (7% to 10%)

Flatulence (1% to 3%)

Nausea (21% to 32%)

Vomiting (3% to 6%)

Xerostomia (6% to 8%)

Neurologic Effects

Dizziness (6% to 9%)

Psychiatric Effects

Dream disorder (up to 3%)

Reproductive Effects

Sexual dysfunction (22% to 34%, in men and 16% to 29% in women)

Rare but Serious Effects

Hyponatremia (reported in 1 patient during a short-term, controlled study of patients with major depressive disorder)

Bleeding (studies and case reports have linked the use of drugs that interfere with serotonin reuptake. Risk is increased with concomitant use of other drugs that affect coagulation and bleeding.)

Hypomania (< 0.1%)

Mania (< 0.1%)

Suicidal thoughts (use of antidepressants has been linked with suicidal thoughts, especially in the first few months of therapy. Children and adolescents may be at increased risk)

Serotonin syndrome (has been reported with monotherapy and with concomitant use of other drugs that affect serotonin)

Drug Interactions^{1,2,3,4,5}:

Abiraterone Acetate

It may increase the serum concentration of CYP2D6 Substrates.

Agents with Antiplatelet Properties

The effects of antiplatelet agents may be increased.

Ethyl Alcohol/ CNS Depressants

The adverse effects of vortioxetine may be enhanced with concomitant use of alcohol/ CNS depressants. Specifically, psychomotor impairment may be enhanced.

Opioid Analgesics

They may increase the risk of serotonin syndrome by enhancing the serotonergic effects of vortioxetine.

Anticoagulant (agents affecting serotonin)

The serotonergic effects may be increased. This can lead to an increased risk of serotonin syndrome.

Antipsychotics

Serotonergic agents may increase the dopamine blockade. This may increase the risk of neuroleptic malignant syndrome. Additionally, antipsychotics may increase serotonergic effects and increase the risk of serotonin syndrome.

Benzodiazepines (metabolized by oxidation)

The metabolism of these the metabolism of benzodiazepines may be reduced with concomitant use of Selective Serotonin Reuptake Inhibitors.

Beta-Blockers

SSRIs may increase the serum concentrations of some beta-blockers. The exceptions to this interaction include acebutolol, atenolol, betaxolol (ophthalmic); betaxolol (systemic), bisoprolol, carteolol (ophthalmic), esmolol, labetalol, levobunolol, metipranolol, nadolol, penbutolol, and sotalol.

Buspirone

This drug may enhance the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Carbamazepine

Carbamazepine may increase the metabolism of vortioxetine. Conversely, the metabolism of carbamazepine may be decreased.

Cimetidine

This may decrease the metabolism of SSRIs.

Clozapine

The serum concentrations of clozapine may be increased.

Cobicistat

The serum concentrations of SSRIs may be increased.

CYP2D6 Inhibitors

These medications may decrease the metabolism/increase serum concentrations of vortioxetine.

CYP3A4 Inducers

These medications may decrease the metabolism/increase serum concentrations of vortioxetine.

Dabrafenib

The serum concentrations of CYP3A4 substrates may be increased.

Darunavir

The serum concentrations of CYP2D6 substrates may be increased.

Dasatinib

This medication may enhance antiplatelet properties.

Deferasirox

The serum concentrations of CYP3A4 substrates may be decreased.

Desmopressin

The adverse or toxic effects of this medication may be increased by SSRIs.

Dextromethorphan

SSRI may enhance the serotonergic effects of this medication. Additionally the serum concentrations of dextromethorphan may be increased.

Galantamine

The metabolism may be decreased by SSRIs.

Hypoglycemic Agents

SSRIs may enhance the hypoglycemic effects/serum concentrations of hypoglycemic agents.

Iobenguane I 123

SSRIs may diminish the therapeutic effects of this agent.

Ioflupane I 123

SSRIs may diminish the therapeutic effects of this agent.

Linezolid

This agent may increase the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Lithium

This agent may increase the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Macrolide Antibiotics

These drugs may enhance the metabolism of SSRIs. Exceptions to these interactions are azithromycin, fidaximicin, and spiramycin.

MAO Inhibitors

These medications may enhance the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Methadone

SSRIs may decrease the metabolism of this medication.

Methylene Blue

SSRIs may enhance the serotonergic effects of this medication and increase the risk of serotonin syndrome.

Metoclopramide

This medication may enhance the adverse or toxic effects of vortioxetine.

Peginterferon Alfa-2b

This medication may decrease the serum concentration of CYP 2D6 substrates.

Pimozide

SSRIs may increase the adverse or toxic effects of this medication.

Quinidine

SSRIs may decrease the metabolism of this medication.

Risperidone

SSRIs may decrease the metabolism of this medication.

Serotonin Modulators

These medications may enhance the adverse or toxic effects of other serotonin modulators and increase the risk for serotonin syndrome.

Thiazide Diuretics

SSRIs may enhance the hyponatremic effects of these medications.

Thyroid Products

The therapeutic effects of these medications may be decreased by SSRIs.

Tocilizumab

This medication may decrease the serum concentrations of CYP3A4 substrates.

Tramadol

SSRIs may enhance the neurotoxic and seizure-potentiating effects of this medication. Additionally, tramadol may enhance the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Tryptophan

This medication may enhance the serotonergic effects of SSRIs and increase the risk of serotonin syndrome.

Dosing/Administration ^{2,3,4,5}

Adult Dosing

Initial dose: 10 mg once daily without regard to meals.

Dosage titration: Increase the dosage up to 20 mg by mouth once daily as tolerated.

Notes: The 20 mg dose has been associated with better treatment effects. The 10 mg dose may be decreased to 5 mg if the patient is intolerant.

Pediatrics

The safety and efficacy has not been evaluated in the pediatric population.

Elderly

No dosage adjustments are necessary in the elderly populations. Caution should be taken as serotonergic antidepressants have been associated with a greater risk of hyponatremia in the elderly.

Renal impairment

There are no dosage adjustments required for impaired renal function.

Hepatic impairment

No dosage adjustments are required in patients with mild to moderate hepatic impairment. Use of vortioxetine is not recommended in patients with severe hepatic impairment.

Use in special circumstances:

Overdosage: ^{5,6} There is no specific antidote known for vortioxetine. Call the poison control center for the latest updates. In the absence of drug specific guidelines some general options include activated charcoal, gastric lavage, or whole gut irrigation. Maintain the patient's airway and provide supportive care.

Conclusion:

Vortioxetine appears to be an effective agent for treating major depressive disorder. However, it has not consistently shown efficacy in the treatment of general anxiety disorder. Overall the medication appears to be relatively safe, however, like many psychiatric medications it has a broad spectrum of side effects and interactions. As a newly approved antidepressant, its place in therapy has not been fully established, but the drug's unique mechanism of action may prove clinically useful with further studies. This medication should not be used as a first-line agent.

Brand name status makes vortioxetine more costly than some of the other options and it has not shown any clear advantage over any comparable antidepressants on the market. Vortioxetine's role should be in patients that are not responding to other medications.

Recommended References:

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