THE AMERICAN PSYCHIATRIC ASSOCIATION

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
BRINTELLIX (vortioxetine) tablets, for oral use

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 *[see Warnings and Precautions]*.

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 *[see Warnings and Precautions]*.

BRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations]*.

INDICATIONS AND USAGE

Major Depressive Disorder

BRINTELLIX is indicated for the treatment of major depressive disorder (MDD). The efficacy of BRINTELLIX was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults.

CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with BRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Warnings and Precautions]*.

  Starting BRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

The risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1* of the BRINTELLIX Full Prescribing Information, which states: 14 additional cases in patients under the age of 18, 5 additional cases in patients between 18 and 24 years of age. There was 1 fewer case in patients between 25 and 64 years of age and 6 fewer cases in patients 65 years of age and over.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

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.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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, 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 for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms 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. It should be noted that BRINTELLIX is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants 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 (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of BRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. BRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking BRINTELLIX. BRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications]*.

If concomitant use of BRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with BRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including BRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this 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 drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions].*

Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in <0.1% of patients treated with BRINTELLIX in pre-marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. 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 treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with BRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of BRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions]*
- Serotonin Syndrome *[see Warnings and Precautions]*
- Abnormal Bleeding *[see Warnings and Precautions]*
- Activation of Mania/Hypomania *[see Warnings and Precautions]*
- Hyponatremia *[see Warnings and Precautions]*

Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure
BRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-marketing clinical studies; 2616 of those patients were exposed to BRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to BRINTELLIX in a 24 week to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12-month open-label studies. A total of 2586 patients were exposed to at least one dose of BRINTELLIX in open-label studies, 1727 were exposed to BRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment
In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies
The most commonly observed adverse reactions in MDD patients treated with BRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any BRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

***Table 2* of the BRINTELLIX Full Prescribing Information shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any BRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6- to 8-week placebo-controlled studies.** The following values from *Table 2* show the percentage of patients exhibiting the adverse reaction while receiving BRINTELLIX 5 mg (N=1013), 10 mg (N=699), 15 mg (N=449), 20 mg (N=455), and placebo (N=1621) respectively. Gastrointestinal Disorders: Nausea (21%, 26%, 32%, 32%, vs. 9%); Diarrhea (7%, 7%, 10%, 7%, vs. 6%); Dry Mouth (7%, 7%, 6%, 8%, vs. 6%); Constipation (3%, 5%, 6%, 6%, vs. 3%); Vomiting (3%, 5%, 6%, 6%, vs. 1%); Flatulence (1%, 3%, 2%, 1%, vs. 1%); Nervous System Disorders: Dizziness (6%, 6%, 8%, 9%, vs. 6%); Psychiatric Disorders: Abnormal Dreams (<1%, <1%, 2%, 3%, vs. 1%); Skin and Subcutaneous Tissue Disorders: Pruritus (including pruritus generalized) (1%, 2%, 3%, 3%, vs. 1%).

Nausea
Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2).* It was usually considered mild or moderate in intensity and the median duration was 2 weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of BRINTELLIX treatment with 15 to 20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking BRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction
Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MDD 6 to 8 week controlled trials of BRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

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 3* 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.

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), the following values from ***Table 3* of the BRINTELLIX Full Prescribing Information show the ASEX incidence of patients who developed treatment-emergent sexual dysfunction** when treated with BRINTELLIX or placebo in any fixed-dose group. The incidence in female patients treated with BRINTELLIX 5 mg (N=65), 10 mg (N=94), 15 mg (N=57), 20 mg (N=67) or placebo (N=135), respectively was 22%, 23%, 33%, 34% vs. 20%. For male patients, the incidence of treatment-emergent sexual dysfunction when treated with BRINTELLIX 5 mg (N=67), 10 mg (N=86), 15 mg (N=67), 20 mg (N=59) or placebo (N=162), respectively was 16%, 20%, 19%, 29% vs. 14%. Incidence was based on the 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. The sample size for each dose group was the number of patients without sexual dysfunction at baseline. Physicians should routinely inquire about possible sexual side effects.

Adverse Reactions Following Abrupt Discontinuation of BRINTELLIX Treatment
Discontinuation symptoms have been prospectively evaluated in patients taking BRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of BRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests
BRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of BRINTELLIX *[see Warnings and Precautions].* In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to BRINTELLIX during the initial 12-week, open-label phase, there were no clinically important changes in lab test parameters between BRINTELLIX and placebo-treated patients.

Weight
BRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to BRINTELLIX during the initial 12-week, open-label phase, there was no significant effect on body weight between BRINTELLIX and placebo-treated patients.

Vital Signs
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.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 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.

Ear and labyrinth disorders — vertigo
Gastrointestinal disorders — dyspepsia
Nervous system disorders — dysgeusia
Vascular disorders — flushing

DRUG INTERACTIONS

CNS Active Agents

Monoamine Oxidase Inhibitors
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs
Based on the mechanism of action of BRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when BRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if BRINTELLIX is co-administered with other serotonergic drugs. Treatment with BRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions]*.

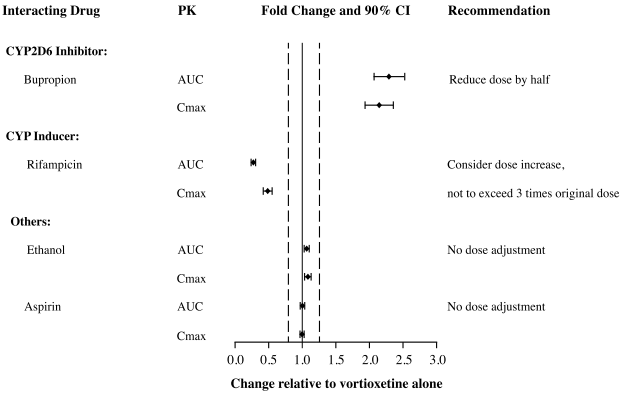
Other CNS Active Agents
No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of BRINTELLIX. Multiple doses of BRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that BRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg). Details on the potential pharmacokinetic interactions between BRINTELLIX and bupropion can be found in Section 7.3, **Potential for Other Drugs to Affect BRINTELLIX**.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of BRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions]*. Coadministration of aspirin 150 mg/day with multiple daily doses of BRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when BRINTELLIX is initiated or discontinued *[see Warnings and Precautions]*.

Potential for Other Drugs to Affect BRINTELLIX
Reduce BRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the BRINTELLIX dose when a strong CYP inducer (e.g., rifampicin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose (*Figure 1*).

Figure 1. Impact of Other Drugs on Vortioxetine PK



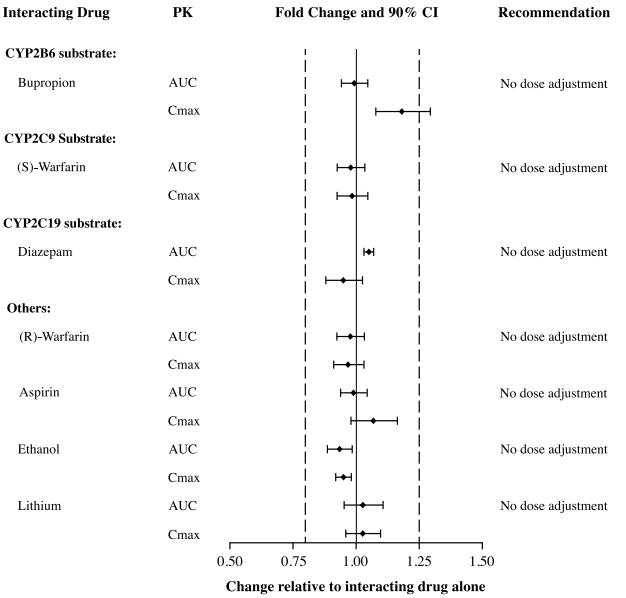
Potential for BRINTELLIX to Affect Other Drugs
No dose adjustment for the comedications is needed when BRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinid), CYP2C9 (e.g., S-warfarin), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine), CYP3A4/5 (e.g., budesonide), and P-gp (e.g., digoxin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and P-gp. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of BRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of BRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2)*.

Because vortioxetine is highly bound to plasma protein, coadministration of BRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, in a clinical study with coadministration of BRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions]*.

Figure 2. Impact of Vortioxetine on PK of Other Drugs



USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies of BRINTELLIX in pregnant women. Vortioxetine caused developmental delays when administered during pregnancy to rats and rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times, the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for BRINTELLIX. All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. BRINTELLIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Neonates exposed to SSRIs or SNRIs, 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, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or possibly, a drug discontinuation syndrome. It should be noted that in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*. When treating a pregnant woman with

BRINTELLIX during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Neonates exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use in pregnancy and PPHN. Other studies do not show a significant statistical association.

A prospective longitudinal study was conducted of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy. When treating a pregnant woman with BRINTELLIX, the physician should carefully consider both the potential risks of taking a serotonergic antidepressant, along with the established benefits of treating depression with an antidepressant.

Animal Data

In pregnant rats and rabbits, no teratogenic effects were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses up to 120 mg/kg (58 times the MRHD) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased at 40 and 120 mg/kg. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

Nursing Mothers

It is not known whether vortioxetine is present in human milk. Vortioxetine is present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from BRINTELLIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Clinical studies on the use of BRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of BRINTELLIX in the pediatric population have not been established.

Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs. young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

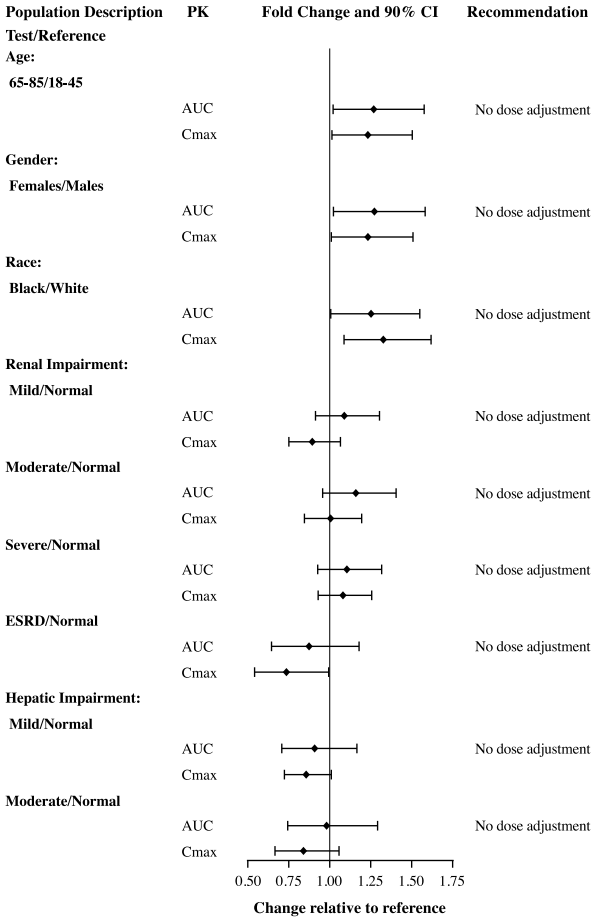
Of the 2616 subjects in clinical studies of BRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Use in Other Patient Populations

No dose adjustment of BRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment *(Figure 3)*. BRINTELLIX has not been studied in patients with severe hepatic impairment. Therefore, BRINTELLIX is not recommended in patients with severe hepatic impairment.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



DRUG ABUSE AND DEPENDENCE

BRINTELLIX is not a controlled substance.

OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with BRINTELLIX. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of BRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of BRINTELLIX in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

Management of Overdose

No specific antidotes for BRINTELLIX are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

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For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. In order for an event to appear in our listing, all notices and changes must be received at least 6 months in advance of the meeting and should be addressed to:

Calendar, American Journal of Psychiatry, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, swestrate@psych.org (e-mail).

Because of space limitations, only listings of meetings of the greatest interest to Journal readers may be included.

FEBRUARY

February 15–18, 25th Annual Meeting of the American Neuropsychiatric Association, Seattle, Wash. www.anpaonline.org (web site).

MARCH

March 12–15, 43rd Annual Meeting of the American Association of Directors of Psychiatric Residency Training, Tucson, Ariz. www.aadprt.org (web site).

MAY

May 3–7, 167th Annual Meeting, American Psychiatric Association, New York, NY. Contact: APA Annual Meetings Dept., 1000 Wilson Blvd, Suite 1825, Arlington, VA 22209; (703) 907-7815 (tel); http://www.psych.org/learn/annual-meeting (web site).

JULY

July 8–13, 28th International Congress of Applied Psychology, Palais de Congrès de Paris, France. Contact exh@icap2014.com (e-mail), www.icap2014.com (web site).

July 30–August 1, 39th Annual University of Colorado Psychiatry Conference, The Gant, Aspen, featuring Glenn Gabbard, M.D., and John Gunderson, M.D., *Good Psychiatric Management*. Contact: Joelynne Jewell, Joelynne.Jewell@ucdenver.edu (e-mail), (303) 724 7401 (tel) for information and brochure.

OCTOBER

October 30–November 2, 66th Institute on Psychiatric Services, San Francisco, CA. www.psychiatry.org/ips (web site).

There's So Much More to AJP Than Meets the Page!

Visit *The American Journal of Psychiatry's* website on PsychiatryOnline for the following features!

AJP in Advance

The very latest research advances!

At **AJP in Advance**, you can discover the following before their appearance in print:

The Clinical Effectiveness of Schema Therapy for Personality Disorders

Schema therapy, an integrative psychotherapy that emphasizes processing negative experiences and using the therapeutic relationships as a way to fulfill unmet needs, was superior to treatment as usual and clarification-oriented psychotherapy in patients with personality disorders, adding to the growing evidence for this combination therapy.

Antidepressant-Induced Liver Injury

There are no strategies yet for preventing antidepressant-induced adverse hepatic events, but early detection by aminotransferase surveillance is essential, as drug-induced liver injury from antidepressants, although rare, may be irreversible in at-risk patients. Age and polypharmacy are two of several critical factors to consider when prescribing antidepressants.

AJP CME

Three articles in this issue form the basis of a short course with questions that can be answered for up to 1 *AMA PRA Category 1 Credit™* each by visiting **http:/psychiatryonline.org/cme.aspx** and clicking on the "**American Journal of Psychiatry**" tab.

CME credit is issued only online, and a paid subscription to AJP CME course program is required. This month's courses appear on pages 245–248.

Have You Heard?

AJP Audio

With AJP Audio you can listen to highlights of this issue. This month, Deputy Editor Susan Schultz presents two trials of lurasidone used in bipolar depression as monotherapy and as adjunctive treatment, relates how anxiety disorders mediate psychotherapy outcome in bipolar depression, introduces a computerized adaptive test for measuring anxiety, reports the risk of autoimmune diseases in individuals with schizophrenia, describes the effects on memory of knowing one's APOE genotype, and identifies genetic, family, and community risk factors for drug abuse.

Revisit the field's rich history!

50 years ago this month: Message From the President of the United States Relative to Mental Illness and Mental Retardation

John F. Kennedy

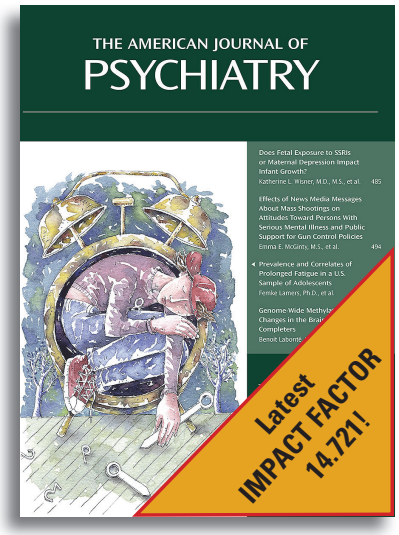
THE AMERICAN JOURNAL OF

PSYCHIATRY

The most widely read psychiatric journal in the world!

The American Journal of Psychiatry (AJP) latest Impact Factor is 14.721, a nearly 2 point rise from last year's 12.759 according to the recently released 2012 Journal Citation Reports® (Thomson Reuters, 2013). AJP, a publication of the American Psychiatric Association, ranks second among 135 journals in psychiatry.

- *The American Journal of Psychiatry* is again among the top journals in psychiatry in terms of immediacy according to Thomson Scientific's Immediacy Index. This important performance metric is a good measure of how quickly a given journal's articles are cited—AJP's placement is a result of publishing articles that are relevant, covering current "hot" topics and cutting-edge research, and getting these findings to the field faster with AJP in Advance, the Journal's online-ahead-of-print publication protocol.



- And, as it has for many years, AJP remains far and away the leader among psychiatric publications in total citations. It's 42,730 citation count was almost 5,000 citations above the next publication.
- The editors of *NEJM Journal Watch Psychiatry* announced the 10 top psychiatry stories in 2013, and SIX were based on articles published in *The American Journal of Psychiatry*! That the majority of the list's selections came from AJP reflects the journal's commitment to publishing articles that deliver clinically important information to the field.

Here are the stories, along with the issue in which the original article appeared:

- Prazosin for PTSD Symptoms and Nightmares in Active-Duty Combat Soldiers (September 2013)
- Varenicline: Fewer Adverse Events Than Previously Thought (December 2013)
- The Question of Ketamine in Treatment-Resistant Depression (October 2013)
- Folate for Treatment-Resistant Depression (December 2012)
- Higher-Dose Citalopram and the FDA Warnings: Not Much to Worry About? (June 2013)
- Do Antipsychotics Hasten Poor Outcomes in Patients with Alzheimer Disease? (September 2013)

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Cover picture

Melancholia (2004) by Sarvenaz Keyhani (b. 1977)

Originally from Iran, I learned to paint when I was 18. I had an exhibition of my work in Tehran in 2000. I trained in psychiatry in Wessex from 2006 to 2009 and since then have been working as a Staff Grade Psychiatrist in Leeds. One of my paintings, *Before the Meeting*, was published in the April 2011 issue of the *Journal* (vol. 198, p. 252). I am a figurative painter and use oil, chalk and oil pastel. In *Melancholia*, the white and black colours serve to intensify the melancholic feeling; depression makes everything bleak and colourless. The woman in the painting brings her knees up to her chest; she is withdrawing from the world. The colour purple is meant to signal the hope that she will recover.

We are always looking for interesting and visually appealing images for the cover of the *Journal* and would welcome suggestions or pictures, which should be sent to Dr Allan Beveridge, British Journal of Psychiatry, 21 Prescot Street, London E1 8BB, UK or bjp@rcpsych.ac.uk.

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BIMONTHLY

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