Like many persons who are concerned about the future of our healthcare delivery system, I have been carefully following the evolving literature and evidence on the patient-centered medical home (PCMH). I would therefore like to share with you a “hunch” I have about the future of PCMHs, with a special emphasis on an assessment of the current evidence about their effectiveness and long-term implications.

Alexander and colleagues assessed the policy context of PCMHs from the perspective of primary care providers.1 Let us begin by defining our terms. The PCMH is described by joint principles agreed upon by several professional societies. In essence, these include (1) a personal physician, (2) a physician-directed medical practice, (3) whole person orientation, (4) coordinated care, (5) an emphasis on quality and safety, (6) improved access, and (7) some changes in the payment system.

It is true, say Alexander and colleagues, that medical home models vary greatly in their practice and structure, “but their success is assumed to rest fundamentally on the ability to focus the work of a defined team on the needs of a patient or family, recruiting social services, specialty medical services, and patient capabilities to solve problems and coordinate care.”

Through qualitative, semistructured, in-person interviews with key representatives of physician organizations and multiple primary care practices that were pursuing the creation of a PCMH, Alexander and his colleagues come to a sobering conclusion.

In essence, they found that “providers’ motivation to embrace the PCMH and their level of confidence regarding the results of such change are greatly influenced by their perception of the external environment and the control they believe they have over this environment.” More simply, Alexander and colleagues found that to turn a typical small primary care practice into a PCMH-designated center requires truly transformational change and a considerable amount of costly resources and organizational support that are not currently readily available.1 What I took away from the analysis by Alexander and colleagues is that it may be impossible to help providers recognize that unnecessary testing is a cost burden to the healthcare system rather than an income stream, without some kind of intervention from a large organization, such as a hospital-based integrated delivery system, managed care plan, or similar entities.

A later study by Fifield and colleagues added to my hunch that this transformation will not be easily or readily achievable.2 In their randomized controlled trial, Fifield and her team found that, regardless of size, “practices can make rapid and sustained transition to a PCMH when provided external supports, including practice redesign, care management and payment reform. Without such supports, change is slow and limited in scope.” In my assessment, given the current environment, we could rationally expect that such change would come quite slowly to the average primary care practice. Fifield and her colleagues had embedded personnel at the practice sites they studied for months, to facilitate the transition to a PCMH,2 knowing that physicians have little direct experience in instituting patient self-management programs and performance reporting and improvement scorecards on their own.

Finally, in a systemic review of the PCMH, Jackson and his colleagues concluded that “the PCMH holds promise for improving the experiences of patients and staff and potentially for improving care processes, but current evidence is insufficient to determine effects on clinical and most economic outcomes.” So there you have it. The way I see it, and based on my review of the evidence, there is much more to this PCMH transition than the average practice could essentially handle on its own at this time.

From a broader policy perspective, this means that integrated delivery systems, seeking to pivot from filling beds to caring for populations, are going to be woefully unprepared for this transition if they rely too heavily on a strategy of building National Committee for Quality Assurance (NCQA)-certified PCMH structures.

Another hunch I have is that most well-trained, well-meaning, hardworking primary care physicians have no “on the ground” sense of what many of the healthcare reform-associated changes will truly mean. Jackson and his team concluded their review by noting that although “implementing the PCMH principles is something to be considered by organizations seeking to enhance patient experience and quality of care, no menu is yet available for specific actions that are most likely to enhance benefits to patients, staff, and organizations.”

Continued
Well, I do have another hunch: if no “menu” is yet available, how can we choose a particular meal? If randomized controlled trials on PCMH implementation do not specifically identify the components of this much-needed menu, what are practices supposed to do?

The drive to create accountable care organizations has obscured our vision at the ground level. It is my hunch that the PCMH, as the building block of an accountable system, is truly where the core challenge lies.

We have not seen the end, or maybe even the beginning, of the PCMH movement. We have missed the central tenet—without physician leadership and physician commitment to organizational change (2 arenas where most clinicians have little formal training), PCMHs are bound to fail. And this, of course, calls into question the greater strategy of accountability and population-based medicine.

The drive to create accountable care organizations has obscured our vision at the ground level. It is my hunch that the PCMH, as the building block of an accountable system, is truly where the core challenge lies. Even as multiple specialty societies embrace the PCMH nomenclature, and as NCQA provides us with a greater number of operational measures, we are a long way from having the leadership skills and organizational understanding that clinicians will need to effectively implement this core strategy for reform.

References
The efficacy and safety of BRINTELLIX in the treatment of MDD was established in:

- **6 short-term (6- to 8-week) randomized, double-blind, placebo-controlled, fixed-dose studies** (including a dedicated study in the elderly) based on mean change from baseline to endpoint in MADRS or HAM-D_17_ total scores.
- **1 long-term (24- to 64-week) maintenance study** in adults based on time to recurrence of depressive episodes.
- In clinical studies, the most common adverse reactions (incidence ≥5% and at least twice the rate of placebo in 6- to 8-week studies) were nausea, constipation, and vomiting.
- In pooled 6- to 8-week placebo-controlled studies, the incidence of patients who received BRINTELLIX and discontinued because of adverse reactions ranged from 5% to 8% over the 5 to 20 mg/day doses compared to 4% for placebo; nausea was the most common adverse reaction reported as a reason for discontinuation.

*Recurrence of a depressive episode is defined as MADRS total score ≥22 or lack of efficacy as judged by the investigators.*

Please visit BRINTELLIXHCP.com to learn more.

**INDICATION**

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

**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 and abrupt, or 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 or 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, coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness), 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 of 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 hallucinations, syncope, seizures, 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 ≥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 (5%, 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.


Please see adjacent pages for Brief Summary of Prescribing Information and visit BRINTELLIXHCP.com for full Prescribing Information and Medication Guide.
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 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 patients who took antidepressant drugs were 4 to 6 times more likely to become suicide attempters than placebo recipients. The risk differences (drug vs. placebo) were absolute risk differences of 1 to 2 per 1,000 patients treated across studies and were statistically significant in most studies. If the risk of suicidal behavior or suicidal ideation appears to be imminent, it should always be considered to outweigh the risk of not treating. The decision to treat with antidepressant medications should be made on the basis of a thorough risk/benefit assessment. This assessment should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and other psychiatric disorders. If, during the course of treatment with an antidepressant, the patient has worsening or emergence of suicidality or unusual changes in behavior, the possibility of a serious drug interaction or other concomitant illness should be considered. Depression is a known risk of suicide. The risk of suicide is highest within the first few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The risk of suicidal behavior with antidepressants increased in short-term studies in patients whenever there was an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients aged 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, most clinical 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 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].

SCREENING PATIENTS FOR SUICIDAL IDEATION AND BEHAVIOR

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 emergence of symptoms such as 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 suicide 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 worsening or who are experiencing emerging 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 or hypomanic 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, any prior suicidal or 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 serotonin (SERT) inhibitors, including SSRI’s, SNRIs, MAOIs, and tricyclic antidepressants (TCA’s). This syndrome is more likely to occur when used alone but more often when used concomitantly with other serotoninergic 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, diarrhea, 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 [see Warnings and Precautions].

If concomitant use of BRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort is clinically warranted, patients should be monitored for the emergence of serotonin syndrome. Patients should be monitored for the emergence of serotonin syndrome.

Abnormal Bleeding
The use of drugs that interfere with serotonin reuptake, 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 number 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 hyponatremia as a result of treatment 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, and confusion. Hyponatremia can also cause 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 labeling:
- 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 the rates 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 6 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 a portion of the 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 BRINTELLIX 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 22% 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. 5%); Dry Mouth (7%, 7%, 6%, 6%, vs. 6%); Constipation (3%, 5%, 6%, 6%, vs. 6%); 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%, <1%, 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 are often observed as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MD 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 admission symptoms such as headache may be difficult 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) ability to achieve 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 in 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=65), 10 mg (N=67), 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 ≥12; 2) any single item ≥2; 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. Discontinuation symptoms were defined as any symptom that occurred in patients without sexual dysfunction at baseline, except for symptoms related to sexual dysfunction (see Warnings and Precautions). Difference between the final and pre-dose symptom severity score was ≥19; 2) any single item ≥2; 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. Because voluntarily reported adverse sexual reactions are known to be underreported, it is possible that some patients may have experienced symptoms such as headaches, 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, open-label 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.

Ears and Labyrinth Disorders — Vertigo
Gastrointestinal Disorders — Dyspepsia
Nervous System Disorders — Dysgeusia
Vascular Disorders — Flushing

DRUG INTERACTIONS

CNS Active Agents

Monoamine Oxidase Inhibitors
Adverse reactions 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 serotonin 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 buspirone 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., rifampin, 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

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>PK</th>
<th>Fold Change and 95% CI</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>CYP2D6 Inhibitor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>AUC</td>
<td>Reduce dose by half</td>
<td></td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP Inhibitor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>AUC</td>
<td>Consider dose increase.</td>
<td></td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td>not to exceed 3 times original dose</td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>AUC</td>
<td>No dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>AUC</td>
<td>No dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 2. Impact of Vortioxetine on PK of Other Drugs

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>PK</th>
<th>Fold Change and 95% CI</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>CYP2B6 substrate:</td>
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<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9 Substrate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S)-Warfarin</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9 substrate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicoumarol</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Crmax</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R)-Warfarin</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Crmax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
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<tr>
<td>Crmax</td>
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<tr>
<td>Ethanol</td>
<td>AUC</td>
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<tr>
<td>Crmax</td>
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<tr>
<td>Lithium</td>
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<td>No dose adjustment</td>
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<tr>
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</tbody>
</table>

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, hyperpyrexia, hypertension, 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/m² basis. Developmental delay, seen 120 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased 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 years of age or older. 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.

DRUG ABUSE AND DEPENDENCE
BRINTELLIX is not a controlled substance.

OVERDOSAGE
Human Experience
There is limited clinical trial experience regarding human overdose 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 overdose, 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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