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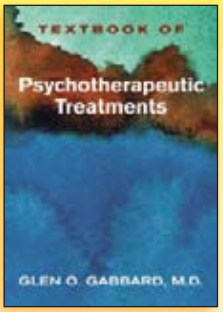

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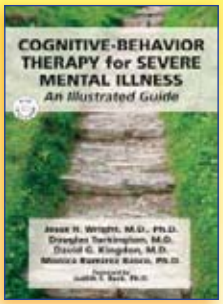

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Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or in patients with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients.**

Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.

On discontinuation, adverse events, some of which may be serious, have been reported with SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics).

Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA_{1c} in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=4843 vs 3048) were: nausea, dry mouth, somnolence,* constipation,* decreased appetite,* and increased sweating.

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

See Brief Summary of full Prescribing Information, including Boxed Warning, on following spread.

* Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for MDD on mean change in HAM-D_{17} Total Score,[1] Maier Subscale,[1] Psychic Anxiety,[1] and Visual Analog Pain Scales.[2] Full antidepressant response may take 4-6 weeks. MMRM=Mixed-effects Models Repeated Measures analysis

References: 1. Data on file, Lilly Research Laboratories: CYM20070220C. **2.** Fava M, et al. *J Clin Psychiatry*. 2004;65(4):521-530.

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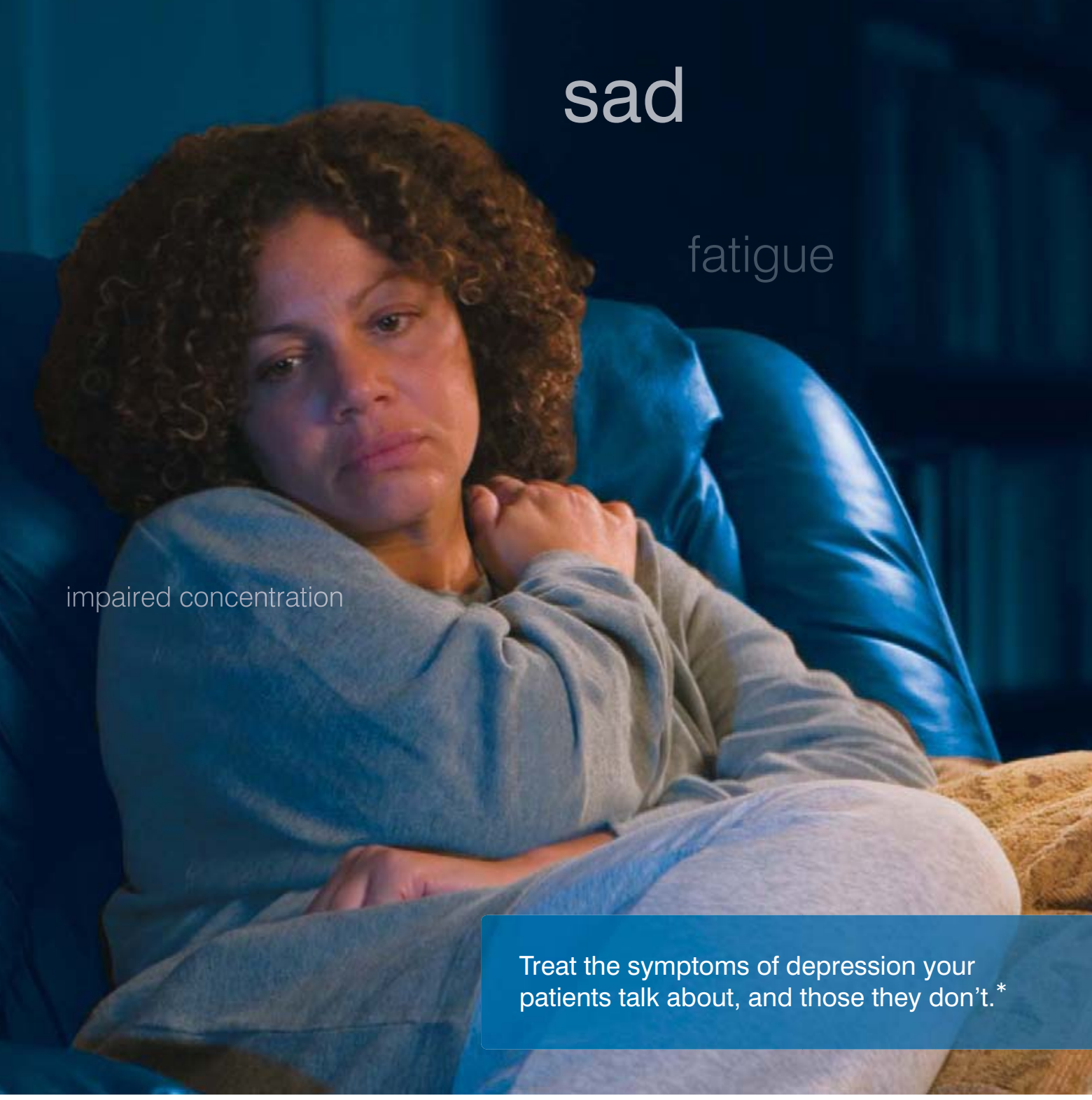

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Brief Summary: Consult the package insert for complete prescribing information.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. *[See Warnings and Precautions and Use in Specific Populations.]*

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD).

Generalized Anxiety Disorder—Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD).

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions]*.

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[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 trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (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 reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 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 of 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.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, 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 trials 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 major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either 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.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms *[see Warnings and Precautions, Discontinuation of Treatment with Cymbalta]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder 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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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 trials) 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 Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions and Drug Interactions]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, warfarin, and other anti-coagulants 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

Cymbalta® (duloxetine hydrochloride) PV 5909 AMP

serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, or fibromyalgia placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/9445) of patients treated with duloxetine and 0.01% (1/6770) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions, Vital Sign Changes]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta—*CYP1A2 Inhibitors*—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs—*Drugs Metabolized by CYP2D6*—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

Other Clinically Important Drug Interactions—*Alcohol*—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), GAD (N=668), DPNP (N=568) and FM (N=876). The population studied was 17 to 89 years of age; 64.8%, 64.7%, 38.7%, and 94.6% female; and 85.5%, 84.6%, 77.6%, and 88% Caucasian for MDD, GAD, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

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 trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.5% (171/876) of the patients who received duloxetine in 3 to 6 month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Adverse Reactions Occurring at an Incidence of 5% or More and at least Twice Placebo Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite.

In addition to the adverse reactions listed above, DPNP trials also included dizziness and asthenia.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine- Treated Patients in Placebo-Controlled Trials—The incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=4843 Cymbalta; N=3048 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo were: nausea, headache, dry mouth, fatigue (includes asthenia), insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), dizziness, somnolence* (includes hypersomnia and sedation), constipation*, diarrhea, decreased appetite* (includes anorexia), and hyperhidrosis. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine- Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that occurred in 2% or more of

patients treated with duloxetine and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPNP placebo-controlled trials (N=115 Cymbalta 20 mg once daily; N=228 Cymbalta 60 mg once daily; N=225 Cymbalta 60 mg twice daily; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

Fibromyalgia—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of FM placebo-controlled trials (N=876 Cymbalta; N=535 placebo) and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, dyspepsia; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Immune System Disorders—seasonal allergy; Infections and Infestations—upper respiratory tract infection, urinary tract infection, influenza, gastroenteritis viral; Investigations—weight increased; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Musculoskeletal and Connective Tissue Disorders—musculoskeletal pain, muscle spasm; Nervous System Disorders—headache, dizziness, somnolence (includes hypersomnia and sedation), tremor, paraesthesia, migraine, dysgeusia; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), sleep disorder, abnormal dreams (includes nightmare), orgasm abnormal (includes anorgasmia), libido decreased (includes loss of libido); Reproductive System and Breast Disorders—ejaculation disorder (includes ejaculation failure and ejaculation dysfunction), penis disorder; Respiratory, Thoracic, and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis, rash, pruritus; Vascular Disorders—hot flush.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. See Table 6 in full PI for specific ASEX results.

Vital Sign Changes—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*. Duloxetine treatment, for up to 26-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3-4 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In fibromyalgia studies, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.4 kg compared with a mean weight gain of approximately 0.3 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients *[see Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 27,229 patients were treated with duloxetine. Of these, 29% (7,886) took duloxetine for at least 6 months, and 13.3% (3,614) for at least one year. The following listing is not intended to 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.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Cardiac Disorders—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia; Ear and Labyrinth Disorders—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus; Endocrine Disorders—*Infrequent:* hypothyroidism; Eye Disorders—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance; Gastrointestinal Disorders—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena; General Disorders and Administration Site Conditions—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance; Infections and Infestations—*Infrequent:* gastroenteritis and laryngitis; Investigations—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased; Metabolism and Nutrition Disorders—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia; Musculoskeletal and Connective Tissue Disorders—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching; Nervous System Disorders—*Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria; Psychiatric Disorders—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide; Renal and Urinary Disorders—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.; Reproductive System and Breast Disorders—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction; Respiratory, Thoracic and Mediastinal Disorders—*Frequent:* yawning; *Infrequent:* throat tightness; Skin and Subcutaneous Tissue Disorders—*Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis; Vascular Disorders—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions]*.

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) *[see Warnings and Precautions]*.

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding 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 or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions]*.

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption *[see Warnings and Precautions]*.

Cymbalta® (duloxetine hydrochloride) PV 5909 AMP

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions]*.

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended *[see Warnings and Precautions]*.

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions]*.

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen *[see Warnings and Precautions]*.

CNS Drugs—*[see Warnings and Precautions]*.

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (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 SSRIs and SNRIs 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 pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2,418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, 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, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta 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]*.

Gender—The half-life of duloxetine is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[see Warnings and Precautions]*.

Severe Renal Impairment—*[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

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Cymbalta® (duloxetine hydrochloride) PV 5909 AMP

Control acute agitation with

GEODON®

for **Injection** (ziprasidone mesylate)

In schizophrenia. . .

Rapid control* with low EPS[1-4]

- **Low incidence of movement disorders[1-4]**
- **Smooth transition, with continued improvement, from IM to oral therapy[3,4]**
- **May be used concomitantly with benzodiazepines[2,3,5]**

*In 2 pivotal studies vs control, significance was achieved at the 2-hour primary end point (10 mg study) and at the 4-hour primary end point (20 mg study).

GEODON for Injection is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with GEODON is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_c interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

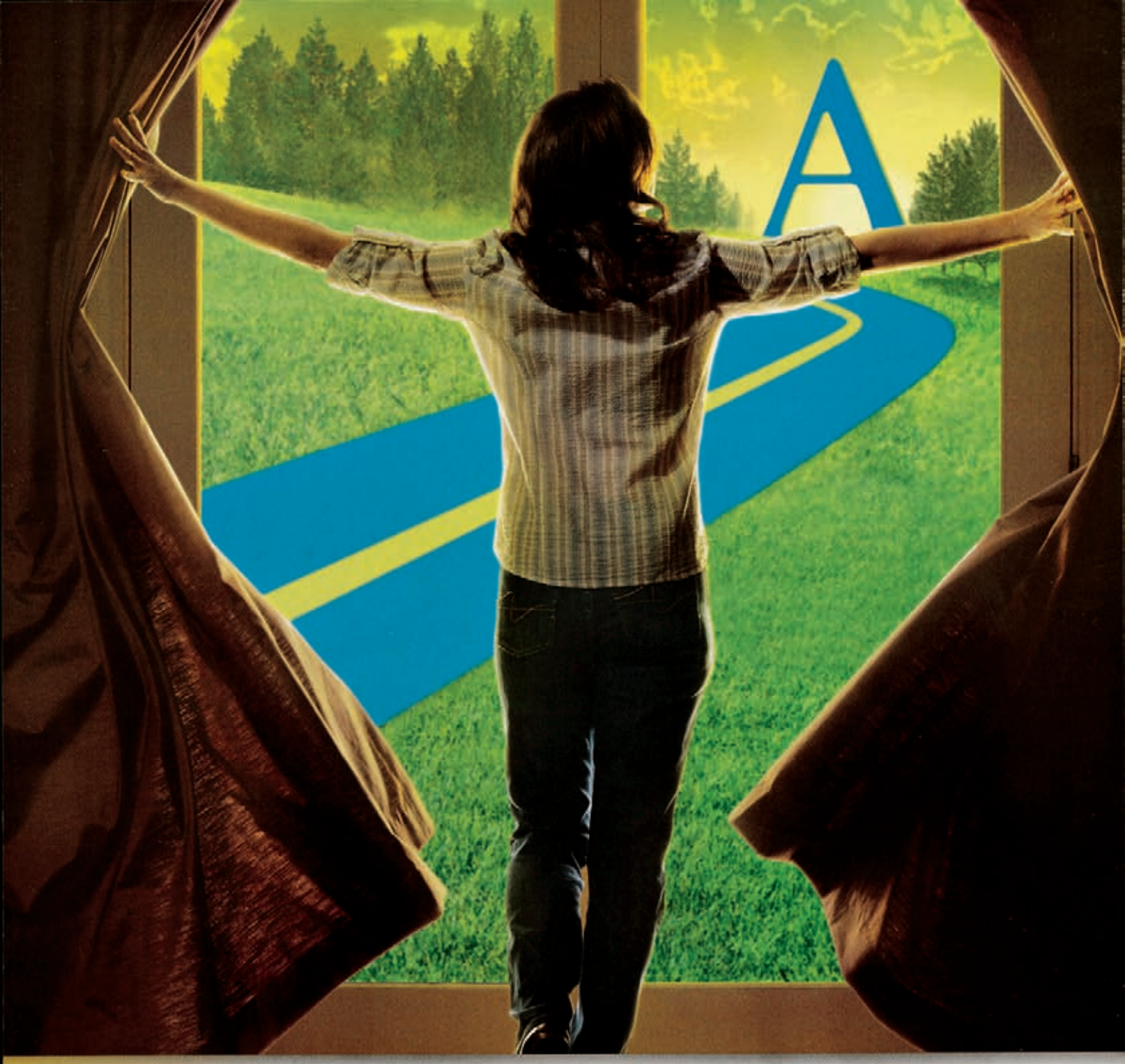
INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — ***QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).** ***QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS —** ***General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —** ***Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—** ***Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

References: 1. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology.* 2001;155:128-134. **2.** Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry.* 2001;62:12-18. **3.** Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology.* 2005;178:514-523. **4.** Brook S, Lucey JV, Gunn KP, for the Ziprasidone IM Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry.* 2000;61:933-941. **5.** Data on file. Pfizer Inc, New York, NY.

Revised November 2006


When symptoms of
Major Depressive
Disorder persist
with treatment



Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression (see Boxed WARNING).

Please see IMPORTANT SAFETY INFORMATION, including

Take the next step to help provide needed relief

The *first and only* adjunctive therapy to antidepressants for adults with Major Depressive Disorder (MDD)[1]

- Significantly improved depressive symptom relief with adjunctive ABILIFY over standard antidepressant therapy alone[2,3]

SIGNIFICANT CHANGE IN MADRS TOTAL SCORE WITH ABILIFY + ADT (LOCF)[3]

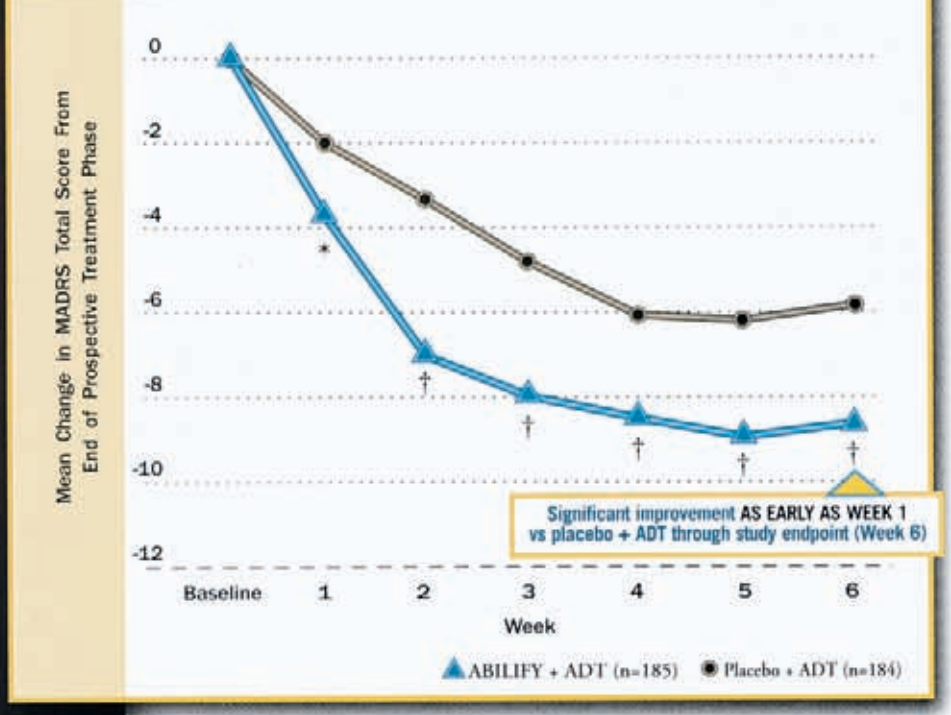


Chart represents one of two registrational trials of adults with nonpsychotic MDD who had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and an inadequate response to 8 weeks of prospective treatment with a leading antidepressant therapy[2,3]

Symptoms measured by MADRS Total Score:

Apparent Sadness
Reported Sadness
Lassitude
Inability to Feel
Concentration Difficulties
Pessimistic Thoughts
Reduced Appetite
Inner Tension
Reduced Sleep
Suicidal Thoughts

MADRS=Montgomery-Asberg Depression Rating Scale.

Adapted from Marcus et al. *J Clin Psychopharmacol.* 2008.

*$P \leq 0.01$ vs placebo.

†$P \leq 0.001$ vs placebo. MADRS Total Score is rated from 0-60. ABILIFY dosing: 5 mg/day starting dose, 15 mg/day maximum dose for patients receiving fluoxetine or paroxetine CR, or 20 mg/day for all other patients.

- In a second registrational trial, significant results were demonstrated as early as Week 2 and continued through study endpoint (Week 6)[3] as measured by mean change in MADRS Total Score
- Few discontinuations due to adverse reactions: ABILIFY + ADT 6% vs placebo + ADT 2%
- In 6-week adjunctive MDD trials, commonly observed adverse reactions of ABILIFY + ADT vs placebo + ADT (≥5% incidence and at least twice the rate of placebo) included akathisia (25% vs 4%), restlessness (12% vs 2%), fatigue (8% vs 4%), insomnia (8% vs 2%), blurred vision (6% vs 1%), and constipation (5% vs 2%)

ABILIFY® (aripiprazole)
2 mg, 5 mg Tablet

HELP ILLUMINATE THE PERSON WITHIN

Boxed WARNINGS, and INDICATION on next page.

IMPORTANT SAFETY INFORMATION and INDICATION for ABILIFY® (aripiprazole)

INDICATION

- ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindication – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

- **Cerebrovascular Adverse Events, Including Stroke** – Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Neuroleptic Malignant Syndrome (NMS)** – As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended
- **Tardive Dyskinesia (TD)** – The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely
- **Hyperglycemia and Diabetes Mellitus** – Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY

Orthostatic Hypotension – ABILIFY may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Seizures/Convulsions – As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment – Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Body Temperature Regulation – Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Suicide – The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Dysphagia – Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo for adjunctive ABILIFY vs adjunctive placebo, respectively):

- Adult patients (with Major Depressive Disorder): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

References: 1. *PDR® Electronic Library™* (n.d.). Greenwood Village, CO: Thomson Micromedex. http://www.thomsonhc.com. Accessed October 16, 2007. 2. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2007;68:843-853. 3. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2008;28:156-165.

Please see BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, on adjacent pages.

ABILIFY® (aripiprazole) 2 mg, 5 mg Tablet

Bristol-Myers Squibb | Otsuka Otsuka America Pharmaceutical, Inc.

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HELP ILLUMINATE THE PERSON WITHIN

ABILIFY® (aripiprazole) Tablets
ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) Oral Solution

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions*].

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression (see *Warnings and Precautions*).

INDICATIONS AND USAGE: ABILIFY (aripiprazole) is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults [see *Clinical Studies (14.3) in Full Prescribing Information*].

CONTRAINDICATIONS: Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis [see *Adverse Reactions*].

WARNINGS AND PRECAUTIONS: Use in Elderly Patients with Dementia-Related Psychosis - Increased Mortality: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*].

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis [see also *Boxed Warning*].

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%], excessive salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole 4%]. The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration [see also *Boxed Warning*].

Clinical Worsening of Depression 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 trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with Major Depressive Disorder (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 reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 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) were reported as **Increases compared to placebo**: <18 (14 additional cases); 18-24 (5 additional cases); and **Decreases compared to placebo**: 25-64 (1 fewer case); ≥65 (6 fewer cases).

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, 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, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials 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 Major Depressive Disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either 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 Major Depressive Disorder 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. Prescriptions for ABILIFY should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 trials) 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 ABILIFY is not approved for use in treating depression in the pediatric population.

Neuroleptic Malignant Syndrome (NMS) - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia - A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY (aripiprazole) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus - Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY [see *Adverse Reactions*]. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with Schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Orthostatic Hypotension - Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures/Convulsions - In short-term, placebo-controlled trials, seizures/convulsions occurred in 0.1% (3/2467) of adult patients treated with oral aripiprazole. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment - ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral ABILIFY (11%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients on oral ABILIFY in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation - Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see *Adverse Reactions*].

Suicide - The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose [see *Adverse Reactions*].

In two 6-week, placebo-controlled studies of aripiprazole as adjunctive treatment of Major Depressive Disorder, the incidences of suicidal ideation and suicide attempts were 0% (0/371) for aripiprazole and 0.5% (2/366) for placebo.

Dysphagia - Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see *Warnings and Precautions* and *Adverse Reactions*].

Use in Patients with Concomitant Illness - Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited [see *Use in Specific Populations*]. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies [see *Warnings and Precautions*].

ADVERSE REACTIONS: Overall Adverse Reactions Profile - The following are discussed in more detail in other sections of the labeling [see *Boxed Warning* and *Warnings and Precautions*]: Use in Elderly Patients with Dementia-Related Psychosis; Clinical Worsening of Depression and Suicide Risk; Neuroleptic Malignant Syndrome (NMS); Tardive Dyskinesia; Hyperglycemia and Diabetes Mellitus; Orthostatic Hypotension; Seizures/Convulsions; Potential for Cognitive and Motor Impairment; Body Temperature Regulation; Suicide; Dysphagia; Use in Patients with Concomitant Illness.

The most common adverse reactions in adult patients in clinical trials (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7819 patient-years of exposure to oral aripiprazole. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure. 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 trials of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience - *Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder:* The following findings are based on a pool of two placebo-controlled trials of patients with Major Depressive Disorder in which aripiprazole was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions was 6% for adjunctive aripiprazole-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions: The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with Major Depressive Disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Less Common Adverse Reactions: The following treatment-emergent reactions reported at an incidence of ≥2%, rounded to the nearest percent, with adjunctive aripiprazole (doses ≥2 mg/day), and at a greater incidence with adjunctive aripiprazole than with adjunctive placebo during short-term (up to 6 weeks), placebo-controlled trials (aripiprazole + ADT n=371; placebo + ADT n=369), respectively, were: akathisia (29%, 4%), restlessness (12%, 2%), fatigue (8%, 4%), insomnia (8%, 2%), somnolence (8%, 4%), upper respiratory tract infection (6%, 4%), blurred vision (4%, 1%), tremor (5%, 4%), constipation (5%, 2%), arthralgia (4%, 3%), dizziness (4%, 2%), sedation (4%, 2%), increased appetite (3%, 2%), weight increased (3%, 2%), disturbance in attention (3%, 1%), feeling jittery (3%, 1%), myalgia (3%, 1%), and extrapyramidal disorder (2%, 0%) ADT = Antidepressant Therapy.

Dose-Related Adverse Reactions:

Extrapyramidal Symptoms: In the short-term, placebo-controlled trials in Major Depressive Disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive aripiprazole-treated patients was 6% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 23% vs. 4% for adjunctive placebo-treated patients. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the Major Depressive Disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: In the 6-week trials of aripiprazole as adjunctive therapy for Major Depressive Disorder, there were no clinically important differences between the adjunctive aripiprazole-treated and adjunctive placebo-treated patients in the median change from baseline in prolactin, fasting glucose, HDL, LDL, or total cholesterol measurements. The median % change from baseline in triglycerides was 5% for adjunctive aripiprazole-treated patients vs. 0% for adjunctive placebo-treated patients.

Weight Gain: In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant treatment. The mean weight gain with adjunctive aripiprazole was 1.7 kg vs. 0.4 kg with adjunctive placebo. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was 5% with adjunctive aripiprazole compared to 1% with adjunctive placebo.

ECG Changes: Between group comparisons for a pooled analysis of placebo-controlled trials in patients with Major Depressive Disorder revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions as defined in *Adverse Reactions* reported by patients treated with oral aripiprazole at multiple doses ≥ 2 mg/day during any phase of a trial within the database of 13,543 adult patients, oral aripiprazole excluding those events already listed as adverse reactions in other parts of *Full Prescribing Information*, or those considered in *Warnings and Precautions*. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Adults: Oral Administration - *Blood and Lymphatic System Disorders:* ≥ *1/1000 patients and <1/100 patients* - leukopenia, neutropenia, thrombocytopenia; *Cardiac Disorders:* ≥ *1/1000 patients and <1/100 patients* - bradycardia, palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischemia; *<1/1000 patients* - atrial flutter, supraventricular tachycardia, ventricular tachycardia; *Eye Disorders:* ≥ *1/1000 patients and <1/100 patients* - photophobia, diplopia, eyelid edema, photopsia; *Gastrointestinal Disorders:* ≥ *1/1000 patients and <1/100 patients* - gastro-esophageal reflux disease, swollen tongue; *esophagitis; <1/1000 patients* - pancreatitis; *General Disorders and Administration Site Conditions:* ≥ *1/100 patients* - asthenia, peripheral edema, irritability, chest pain; ≥ *1/1000 patients and <1/100 patients* - face edema, thirst, angioedema; *<1/1000 patients* - hypothermia; *Hepatobiliary Disorders <1/1000 patients* - hepatitis, jaundice; *Immune System Disorders:* ≥ *1/1000 patients and <1/100 patients* - hypersensitivity; *Injury, Poisoning, and Procedural Complications:* ≥ *1/100 patients* - fall, ≥ *1/1000 patients and <1/100 patients* - self mutilation; *<1/1000 patients* - heat stroke; *Investigations:* ≥ *1/100 patients* - weight decreased, creatine phosphokinase increased, ≥ *1/1000 patients and <1/100 patients* - hepatic enzyme increased, blood glucose increased, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood creatinine increased, blood bilirubin increased; *<1/1000 patients* - blood lactate dehydrogenase increased, glycosylated hemoglobin increased, gamma-glutamyl transferase increased; *Metabolism and Nutrition Disorders:* ≥ *1/100 patients* - decreased appetite; ≥ *1/1000 patients and <1/100 patients* - hyperlipidemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycemia, hypokalemia, hyponatremia, hypoglycemia, polydipsia; *<1/1000 patients* - diabetic ketoacidosis; *Musculoskeletal and Connective Tissue Disorders:* ≥ *1/1000 patients and <1/100 patients* - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; *<1/1000 patients* - rhabdomyolysis; *Nervous System Disorders:* ≥ *1/100 patients* - coordination abnormal; ≥ *1/1000 patients and <1/100 patients* - speech disorder, parkinsonism, memory impairment, cogwheel rigidity, cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia; *<1/1000 patients* - Grand Mal convulsion, choreoathetosis; *Psychiatric Disorders:* ≥ *1/100 patients* - suicidal ideation; ≥ *1/1000 patients and <1/100 patients* - aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, homicidal ideation; *<1/1000 patients* - catatonia, sleep walking; *Renal and Urinary Disorders:* ≥ *1/1000 patients and <1/100 patients* - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥ *1/1000 patients and <1/100 patients* - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; *<1/1000 patients* - gynaecomastia, priapism; *Respiratory, Thoracic and Mediastinal Disorders:* ≥ *1/100 patients* - nasal congestion, dyspnea, pneumonia aspiration; *Skin and Subcutaneous Tissue Disorders:* ≥ *1/100 patients* - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥ *1/1000 patients and <1/100 patients* - pruritus, photosensitivity reaction, alopecia, urticaria; *Vascular Disorders:* ≥ *1/100 patients* - hypertension; ≥ *1/1000 patients and <1/100 patients* - hypotension.

Postmarketing Experience - The following adverse reactions have been identified during post-approval use of ABILIFY (aripiprazole). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

DRUG INTERACTIONS: Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol. Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY - Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole and Other CYP3A4 Inhibitors: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15 mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When ketoconazole is given concomitantly with aripiprazole, the aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; moderate inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Quinidine and Other CYP2D6 Inhibitors: Coadministration of a 10 mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when quinidine is given concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased. When adjunctive ABILIFY is administered to patients with Major Depressive Disorder, ABILIFY should be administered without dosage adjustment as specified in *Dosage and Administration (2.3)* in Full Prescribing Information.

Carbamazepine and Other CYP3A4 Inducers: Coadministration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.

Potential for ABILIFY to Affect Other Drugs - Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. *In vivo* studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. No effect of aripiprazole was seen on the pharmacokinetics of lithium or valproate.

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Drugs Having No Clinically Important Interactions with ABILIFY - Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500 mg/day-1500 mg/day) and aripiprazole (30 mg/day) were coadministered, at steady state the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady-state there were no clinically significant changes in the C_{max} or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200 mg/day-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium. Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

Lamotrigine: Coadministration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients with Bipolar I Disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine.

Dextromethorphan: Aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-desilkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Lorazepam: Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects (n=40; 35 males and 5 females; ages 19-45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone [see *Warnings and Precautions*].

Escitalopram: Coadministration of 10 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

Venlafaxine: Coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

Fluoxetine, Paroxetine, and Sertraline: A population pharmacokinetic analysis in patients with Major Depressive Disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

USE IN SPECIFIC POPULATIONS: In general, no dosage adjustment for ABILIFY (aripiprazole) is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function [see *Dosage and Administration (2.5)* in Full Prescribing Information].

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Labor and Delivery - The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers - Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use - Safety and effectiveness in pediatric patients with Major Depressive Disorder has not been established. The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between aripiprazole and lithium or valproate can be extrapolated from adult data, along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Geriatric Use - In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients [see also *Boxed Warning* and *Warnings and Precautions*].

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1073 patients were diagnosed with Dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole in Major Depressive Disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 52%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment - In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Gender - C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30% to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race - Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking - Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

DRUG ABUSE AND DEPENDENCE - ABILIFY is not a controlled substance.

Abuse and Dependence: Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Patients should be evaluated carefully for a history of drug abuse and closely observed for signs of ABILIFY misuse or abuse.

OVERDOSAGE: 76 cases of deliberate or accidental overdosage with oral aripiprazole alone or in combination with other substances were reported worldwide (44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (myotasis and feeling abnormal)). Additionally, 10 of these cases were in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. The largest known acute ingestion was 1080 mg of oral aripiprazole (36 times maximum recommended daily dose) in a patient who fully recovered. Common adverse reactions (reported in at least 5% of all overdose cases) were vomiting, somnolence, and tremor. **For more information on symptoms of overdose, see Full Prescribing Information.**

Management of Overdosage: No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. ***Charcoal:*** In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%. ***Hemodialysis:*** Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY: [See Medication Guide in Full Prescribing Information.]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - Advise patients and caregivers of increased risk of death [see *Warnings and Precautions*].

Clinical Worsening of Depression and Suicide Risk - Alert families and caregivers of patients to monitor for the emergence of agitation, irritability, unusual changes in behavior, suicidality, and other symptoms as described in *Warnings and Precautions* and to report such symptoms immediately. Advise patients and their families and caregivers to read the Medication Guide and assist them in understanding its contents [see *Warnings and Precautions*].

Interference with Cognitive and Motor Performance - Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely [see *Warnings and Precautions*].

Pregnancy - Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY [see *Use In Specific Populations*].

Nursing - Patients should be advised not to breast-feed an infant if they are taking ABILIFY [see *Use In Specific Populations*].

Concomitant Medication - Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions [see *Drug Interactions*].

Alcohol - Patients should be advised to avoid alcohol while taking ABILIFY [see *Drug Interactions*].

Heat Exposure and Dehydration - Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions*].

Sugar Content - Patients should be advised that each mL of ABILIFY Oral Solution contains 400 mg of sucrose and 200 mg of fructose.

Phenylketonurics - Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT Orally Disintegrating Tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

Tablets manufactured by Otsuka Pharmaceutical Co. Ltd, Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA. Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. US Patent Nos: 5,006,528; 6,977,257; and 7,115,587

Bristol-Myers Squibb Otsuka otsuka america Pharmaceutical, Inc.

Based on 1239550A2, 0308L-1050A D6-B0001A-05-08-MDD 570US08PIS01402 0308L-1113 Rev May 2008

Choose SEROQUEL for bipolar depression

SEROQUEL is the only mood-stabilizing atypical approved to control the depressive symptoms of bipolar disorder[1,2]

Important Safety Information for SEROQUEL

- SEROQUEL is indicated for the treatment of depressive episodes in bipolar disorder; acute manic episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; for the maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex; and schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment and the appropriate dose
- **Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death, compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis (See Boxed Warning)**
- **Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Patients of all ages started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in patients under the age of 18 years (See Boxed Warning)**

For bipolar disorder

Please see additional Important Safety Information on the adjacent pages, and Brief Summary, including Boxed Warnings, adjacent to this ad.

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

SEROQUEL is the only mood-stabilizing atypical approved to control the depressive symptoms of bipolar disorder[1,2]

- SEROQUEL is approved for both the acute and maintenance treatment of bipolar depression*[1]
- SEROQUEL stabilizes mood in both acute mania and bipolar depression[1]
- As adjunct therapy, SEROQUEL helps maintain remission of depressive symptoms*[3]

**Maintenance therapy as adjunct to lithium or divalproex.*

Important Safety Information for SEROQUEL, continued

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing
- A potentially fatal symptom complex, sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include immediate discontinuation of antipsychotic drugs
- Leukopenia, neutropenia, and agranulocytosis (including fatal cases), have been reported temporally related to atypical antipsychotics, including SEROQUEL. Patients with a pre-existing low white blood cell (WBC) count or a history of drug induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. In these patients, SEROQUEL should be discontinued at the first sign of a decline in WBC absent other causative factors. Patients with neutropenia should be carefully monitored, and SEROQUEL should be discontinued in any patient if the absolute neutrophil count is $< 1000/mm^3$
- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of TD

Please see additional Important Safety Information on the adjacent pages, and Brief Summary, including Boxed Warnings, adjacent to this ad.

Important Safety Information for SEROQUEL, continued

- Warnings and Precautions also include the risk of orthostatic hypotension, cataracts, seizures, hyperlipidemia, and possibility of suicide attempts. Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy
- The most commonly observed adverse reactions associated with the use of SEROQUEL versus placebo in clinical trials for schizophrenia and bipolar disorder were dry mouth (9%-44% vs 3%-13%), sedation (30% vs 8%), somnolence (18%-34% vs 7%-9%), dizziness (9%-18% vs 5%-7%), constipation (8%-10% vs 3%-5%), asthenia (5%-10% vs 3%-4%), abdominal pain (4%-7% vs 1%-3%), postural hypotension (4%-7% vs 1%-2%), pharyngitis (4%-6% vs 3%), weight gain (5%-6% vs 1%-3%), lethargy (5% vs 2%), nasal congestion (5% vs 3%), SGPT increased (5% vs 1%), and dyspepsia (5%-7% vs 1%-4%)
- In long-term clinical trials of quetiapine, hyperglycemia (fasting glucose $\geq$ 126 mg/dL) was observed in 10.7% of patients receiving quetiapine (mean exposure 213 days) vs 4.6% in patients receiving placebo (mean exposure 152 days)

For bipolar disorder

References: 1. SEROQUEL Prescribing Information.
2. Data on file, DA-SER-51, AstraZeneca Pharmaceuticals LP.
3. Data on file, 263170, AstraZeneca Pharmaceuticals LP.

263625 6/08 **www.SEROQUEL.com**

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

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SEROQUEL
(quetiapine fumarate)
TABLETS

RX ONLY

BRIEF SUMMARY: For full Prescribing Information, see package insert.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients (see *Warnings and Precautions*).

INDICATIONS AND USAGE

Bipolar Disorder SEROQUEL is indicated for the: • treatment of depressive episodes associated with bipolar disorder; • treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex; and • maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex. ***Depression*** The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients [see **Clinical Pharmacology** in full Prescribing Information (12)]. Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks. ***Mania*** The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania [see **Clinical Pharmacology** in full Prescribing Information (12)]. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy. ***Maintenance Treatment in Bipolar Disorder*** The efficacy of SEROQUEL as adjunct maintenance therapy to lithium or divalproex was established in 2 identical randomized placebo-controlled double-blind studies in patients with Bipolar I Disorder [see **Clinical Studies** in full Prescribing Information (14)]. The physician who elects to use SEROQUEL for extended periods in Bipolar Disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **Dosage and Administration**). **Schizophrenia** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients [see **Clinical Pharmacology** in full Prescribing Information (12)]. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **Dosage and Administration**).

DOSAGE AND ADMINISTRATION

Bipolar Disorder ***Depression*** *Usual Dose:* SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL	50 mg	100 mg	200 mg	300 mg

In these clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however, no additional benefit was seen in the 600 mg group. ***Mania*** *Usual Dose:* When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicate that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials. ***Maintenance*** Maintenance of efficacy in Bipolar I Disorder was demonstrated with SEROQUEL (administered twice daily totalling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase [see **Clinical Studies** in full Prescribing Information (14)]. **Schizophrenia** *Usual Dose:* SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg twice per day was also effective. Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials. **Dosing in Special Populations** Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [see **Clinical Pharmacology** in full Prescribing Information (12)]. When indicated, dose escalation should be performed with caution in these patients. Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (see **Drug Interactions**). **Maintenance Treatment** While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment. **Reinitiation of Treatment in Patients Previously Discontinued** Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed. **Switching from Antipsychotics** There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

CONTRAINDICATIONS

None known

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis (see *Boxed Warning*). 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 trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (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 reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 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.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, 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 trials 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**

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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 major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either 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 major depressive disorder 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 health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. ***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 trials) 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 SEROQUEL is approved for use in treating adult bipolar depression. **Hyperglycemia and Diabetes Mellitus** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine (see **Adverse Reactions, Hyperglycemia**). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. **Neuroleptic Malignant Syndrome (NMS)** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Orthostatic Hypotension** SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (see **Dosage and Administration**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Leukopenia, Neutropenia and Agranulocytosis** In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue SEROQUEL and have their WBC followed until recovery (see **Adverse Reactions**). **Tardive Dyskinesia** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Cataracts** The development of cataracts was observed in association with quetiapine treatment in chronic dog studies [see **Nonclinical Toxicology, Animal Toxicology** in full Prescribing Information (13.2)]. Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. **Seizures** During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Hyperlipidemia** In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol $\geq$240 mg/dL and triglycerides $\geq$200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo treated patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo treated patients respectively. **Hyperprolactinemia** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats [see **Carcinogenesis, Mutagenesis, Impairment of Fertility** in full Prescribing Information (13.1)]. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro,* a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo. **Potential for Cognitive and Motor Impairment** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% of placebo patients. Since SEROQUEL has the potential to impair judgment,

thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%). **Use in Patients with Concomitant Illness** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited [see **Pharmacokinetics** in full Prescribing Information (12.3)]. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Warnings and Precautions**). **Withdrawal** Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including SEROQUEL. Gradual withdrawal is advised.

ADVERSE REACTIONS

Clinical Study Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The information below is derived from a clinical trial database for SEROQUEL consisting of over 4300 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy), 646 patients exposed to SEROQUEL for the maintenance treatment of bipolar I disorder as adjunct therapy, and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 4300 subjects, approximately 4000 (2300 in schizophrenia, 405 in acute bipolar mania, 698 in bipolar depression, and 646 for the maintenance treatment of bipolar I disorder) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 2400 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse reactions for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse reactions for bipolar depression. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials: Bipolar Disorder: Depression: Overall, discontinuations due to adverse reactions were 12.3% for SEROQUEL 300 mg vs. 19.0% for SEROQUEL 600 mg and 5.2% for placebo. ***Mania:*** Overall, discontinuations due to adverse reactions were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. ***Schizophrenia:*** Overall, there was little difference in the incidence of discontinuation due to adverse reactions (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **Warnings and Precautions**).

Adverse Reaction	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Reactions Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

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Table 2. Treatment-Emergent Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)[1]

Body System/Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

1 Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 3 weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)[1]

Body System/Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

1 Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%). Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 8 weeks)

of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo treated patients.

Table 4. Treatment-Emergent Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression[1]

Body System/Preferred Term	SEROQUEL (n=698)	PLACEBO (n=347)
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	5%	3%

1 Reactions for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of these demographic factors. ***Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials*** *Dose-related Adverse Reactions:* Spontaneously elicited adverse reaction data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse reactions. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse reactions: dyspepsia, abdominal pain, and weight gain. ***Adverse Reactions in clinical trials with quetiapine and not listed elsewhere in the label:*** The following adverse reactions have also been reported with quetiapine: abnormal dreams and nightmares, hypersensitivity, restless legs syndrome, and elevations in serum creatine phosphokinase (not associated with NMS). *Extrapyramidal Symptoms: Dystonia: Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates Parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

SEROQUEL

Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse reactions potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. ***Vital Signs and Laboratory Studies*** *Vital Sign Changes* SEROQUEL is associated with orthostatic hypotension [see **Warnings and Precautions**). *Weight Gain* In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo. *Laboratory Changes* An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides. In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed (see **Warnings and Precautions**). In placebo controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $<1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine fumarate, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors (see **Warnings and Precautions**). *Hyperglycemia* In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥126 mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients). In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥200 mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥126 mg/dl was 2.6%. *ECG Changes* Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to >120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **Warnings and Precautions**). ***Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL*** Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, and those reaction terms which were so general as to be uninformative. It is important to emphasize that, although the reactions reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Nervous System:** ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole:** ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged. **Digestive System:** ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System**: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation. **Metabolic and Nutritional System:** ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** ***Frequent:*** sweating; ***Infrequent:*** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses:** ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia. **Endocrine System:** ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism. **Post Marketing Experience** The following adverse reactions were identified during post approval of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported since market introduction

*adjusted for gender

which were temporally related to SEROQUEL therapy include: anaphylactic reaction. Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens-Johnson syndrome (SJS).

DRUG INTERACTIONS

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **Dosage and Administration**). *Divalproex:* Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance. *Thioridazine:* Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. *Cimetidine:* Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. *P450 3A Inhibitors:* Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors). *Fluoxetine, Imipramine, Haloperidol, and Risperidone:* Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs** *Lorazepam:* The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. *Divalproex:* The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. *Lithium:* Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. *Antipyrine:* Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

USE IN SPECIFIC POPULATIONS

Pregnancy The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers** SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use** Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients [see **Clinical Pharmacology** in full Prescribing Information (12) and **Dosage and Administration**].

DRUG ABUSE AND DEPENDENCE

Controlled Substance SEROQUEL is not a controlled substance. **Abuse** SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

SEROQUEL® (quetiapine fumarate) Tablets

OVERDOSAGE

Human Experience In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse reactions or recovered fully from the reported reactions. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drugs known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see **Warnings and Precautions**). One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. **Management of Overdosage** In In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

PATIENT COUNSELING INFORMATION

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL. ***Clinical Worsening and Suicide Risk*** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. ***Increased Mortality in Elderly Patients with Dementia-Related Psychosis*** Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is not approved for elderly patients with dementia-related psychosis. ***Neuroleptic Malignant Syndrome (NMS)*** Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever. ***Hyperglycemia and Diabetes Mellitus*** Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should be monitored. ***Orthostatic Hypotension*** Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose. ***Leukopenia/Neutropenia*** Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL (see **Warnings and Precautions**). ***Interference with Cognitive and Motor Performance*** Patients should be advised of the risk of somnolence or sedation, especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine. ***Pregnancy and Nursing*** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine. ***Concomitant Medication*** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. ***Heat Exposure and Dehydration*** Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

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NEW
Introducing
A NEW SNRI therapy
for major depressive disorder in adults

IMPORTANT TREATMENT CONSIDERATIONS

PRISTIQ 50 mg is indicated for the treatment of major depressive disorder in adults.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients.

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including PRISTIQ, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs that impair the metabolism of serotonin (including MAOIs). If concomitant use is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.

For major depressive disorder in adults

New SNRI therapy. From the start: One dose. No titration.

- The major active metabolite of Effexor XR® (venlafaxine HCl)[1]
- One simple 50-mg dose, no need to titrate[1]
  - Dosage adjustment is necessary in patients with severe renal impairment or end-stage renal disease and is recommended when discontinuing therapy
- PRISTIQ may help your patients with depression—emotionally, physically, and functionally[1-3]
- Discontinuation rate due to adverse events was comparable to placebo in clinical studies at 50 mg[1]

New Pristiq™ desvenlafaxine
EXTENDED-RELEASE TABLETS

- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose (by giving 50 mg of PRISTIQ less frequently) rather than abrupt cessation is recommended whenever possible.
- Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or end-stage renal disease (ESRD). The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and twice the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

References: 1. Pristiq™ (desvenlafaxine) Prescribing Information. Wyeth Pharmaceuticals Inc. **2.** Data on file, Wyeth Pharmaceuticals Inc. **3.** Sheehan DV. Sheehan Disability Scale. In: Rush AJ Jr, Pincus HA, First MB, et al, eds. *Handbook of Psychiatric Measures*. 1st ed. Washington, DC: American Psychiatric Association; 2000:113-115.

Please see brief summary of Prescribing Information on adjacent pages.

Pristiq™ desvenlafaxine

Wyeth®

Pristiq™ desvenlafaxine Extended-Release Tablets

BRIEF SUMMARY. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

WARNING: Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1 in the full prescribing information)]*.

INDICATIONS AND USAGE: Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).

CONTRAINDICATIONS: Hypersensitivity-Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. **Monoamine Oxidase Inhibitors-**Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI *[see Dosage and Administration (2.5) in the full prescribing information]*.

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 (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (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 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 9 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 2 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 of the full prescribing information. 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 major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either 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. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *[see Warnings and Precautions (5.9) and Dosage and Administration (2.3) in the full prescribing information for a description of the risks of discontinuation of Pristiq]*. Families and caregivers of patients being treated with antidepressants for major depressive disorder 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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. 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 Pristiq is not approved for use in treating bipolar depression. **Serotonin Syndrome-**The development of a potentially life-threatening serotonin syndrome may occur with Pristiq treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs). The concomitant use of Pristiq and MAOIs is contraindicated *[see Contraindications (4.2)]*. If concomitant treatment with Pristiq and an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Pristiq with serotonin precursors (such as tryptophan supplements) is not recommended. **Elevated Blood Pressure-** Patients receiving Pristiq should have regular monitoring of blood pressure since dose-dependent increases were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq. Sustained hypertension- Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered *[see Adverse Reactions (6.1)]*. Treatment with Pristiq in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits. In clinical studies, regarding the proportion of patients with sustained hypertension, the following rates were observed: placebo (0.5%), Pristiq 50 mg (1.3%), Pristiq 100 mg (0.7%), Pristiq 200 mg (1.1%), and Pristiq 400 mg (2.3%). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding**-SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma**-Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania**-During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease**-Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders *[see Adverse Reactions (6.1)]*. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation**-Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq *[see Adverse Reactions (6.1)]*. **Discontinuation of Treatment with Pristiq-**Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate *[see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information]*. **Renal Impairment**-In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq *[see Clinical Pharmacology (12.6) in full prescribing information]*. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD *[see Dosage and Administration (2.2) in full prescribing information]*. **Seizure-** Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia-** Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information]*. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine-** Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia-** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

ADVERSE REACTIONS: Clinical Studies Experience: The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥5% and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Adverse reactions reported as reasons for discontinuation of treatment- The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). Common adverse reactions in placebo-controlled MDD studies- Table 3 in full PI shows the incidence of common adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. Cardiac disorders: Palpitations, Tachycardia. Blood pressure increased; Gastrointestinal disorders: Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; General disorders and administration site conditions: Fatigue, Chills, Feeling jittery, Asthenia; Metabolism and nutrition disorders: Decreased appetite, weight decreased; Nervous system disorders: Dizziness, Somnolence, Headache, Tremor, Paresthesia, Disturbance in attention; Psychiatric Disorders: Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; Renal and urinary disorders: Urinary hesitation; Respiratory, thoracic, and mediastinal disorders: Yawning; Skin and subcutaneous tissue disorders: Hyperhidrosis, Rash; Special Senses: Vision blurred; Mydriasis, Tinnitus, Dysgeusia; Vascular Disorders: Hot flush. Sexual function adverse reactions-Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). Men Only: Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; Women Only: Anorgasmia Other adverse reactions observed in premarketing clinical studies: Other infrequent adverse reactions occurring at an incidence of <2% in MDD patients treated with Pristiq were: *Immune system disorders* – Hypersensitivity. *Investigations* – Liver function test abnormal, blood prolactin increased. *Nervous system disorders* – Convulsion, syncope, extrapyramidal disorder. *Psychiatric disorders* – Depersonalization, hypomania. *Respiratory, thoracic and mediastinal disorders* – Epistaxis. *Vascular disorders* – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo *[see Warnings and Precautions (5.7)]*. Discontinuation events-Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥5% include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy *[see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information]*. Laboratory, ECG and vital sign changes observed in MDD clinical studies- The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. *Lipids*-Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant *[see Warnings and Precautions (5.6)]*. *Proteinuria*-Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. *ECG changes*-Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. *Vital sign changes*-Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs *[see Warnings and Precautions (5.13)]*. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI *[see Contraindications (4.2)]*. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems *[see Warnings and Precautions (5.2)]*. **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. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-**There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects – Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), 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 SSRIs and SNRIs 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 (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-**Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-**The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-**Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C002, revised April 2008.

Wyeth®

- **Effectively treats acute manic and mixed episodes**
- **Well-established tolerability profile**
- **Target 120–160 mg/day on Day 2**
- **Initiate dosing at 80 mg/day with meals**

GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic symptoms.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with certain other QT-prolonging drugs. **GEODON has been associated with prolongation of the QT_c interval. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. Patients who are at risk for electrolyte disturbances should have baseline measurements performed before initiating GEODON. Patients on diuretics should be monitored.**

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

In short-term schizophrenia clinical trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo.

Individual results may vary.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON

GEODON®
(ziprasidone HCl) **Capsules**

BRIEF SUMMARY See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Geodon (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — ***QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS** — ***Increased Mortality in Elderly Patients with Dementia-Related Psychosis:*** **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).** ***QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT$_c$ interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT$_c$ interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT$_c$-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT$_c$ from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT$_c$ length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT$_c$ interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2503 (0.08%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT$_c$ intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT$_c$ interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT$_c$ prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT$_c$ prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT$_c$ from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT$_c$ from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT$_c$ from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT$_c$ interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT$_c$ length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT$_c$ interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT$_c$ interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congential long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT$_c$ intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT$_c$ measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS** — ***General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose-related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING. WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine D$_2$ receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT$_c$ prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information* Section should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances, should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT$_c$ measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: Carbamazepine, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg od for 5 days, increased the AUC and C_{max} of GEODON by about 35%–40%. Cimetidine, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of Maalox did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2D1, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with lithium 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 3-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS** — ***Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 9.5% (18/2/9) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events.

Adverse Events at an Incidence ≥ 5% and at Least Twice the Rate of Placebo: The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (21%), extrapyramidal symptoms (21%), dizziness (16%), akathisia (10%), abnormal vision (8%), asthenia (8%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hyperthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS): The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Dystonia:*** Prolonged abnormal contractions of muscle groups may occur in susceptible individuals during first few days of treatment. Dystonia may occur at any dose level but with greater frequency and severity with high potency, and at higher doses of first generation antipsychotic drugs. Elevated risk is observed in males and younger age groups. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (≥7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT$_c$ interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole—*Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System—*Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System—*Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine—*Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System—*Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders—*Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System—*Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System—*Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hyperthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System—*Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages—*Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses—*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System—*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* pyelonephritis, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism.

DRUG ABUSE AND DEPENDENCE — ***Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

Revised: August 2008

IMPORTANT CORRECTION OF DRUG INFORMATION ABOUT EFFEXOR XR® (VENLAFAXINE HCl) EXTENDED-RELEASE CAPSULES

An advertisement in professional journal publications for EFFEXOR XR® (venlafaxine HCl) Extended-Release Capsules for the treatment of major depressive disorder was the subject of a Warning Letter issued by the U.S. Food and Drug Administration (FDA) in December 2007. The FDA stated that the journal ad was misleading because it overstated the efficacy of EFFEXOR XR, made unsubstantiated superiority claims, and contained other unsubstantiated claims regarding EFFEXOR XR.

Wyeth would like to take this opportunity to clarify the content of the advertisement.

Claims that Reference the Baldomero et al Study and Other Related Claims

The FDA objected to the claim, "In an open-label study of patients who failed previous antidepressant treatment, nearly 60% achieved remission when changed to EFFEXOR XR." The FDA determined that the Baldomero study (the cited reference for this claim) could not be relied upon as substantial evidence to support the claim due to the following reasons: (1) the study was an open-label study, which is not an appropriate study design to measure subjective end points because it fails to minimize potential bias; (2) the study did not include a placebo group, so there was no way to determine the actual effect size of the drug; and (3) the study did not provide information about whether EFFEXOR XR was superior to failed therapy because study subjects were not randomized to their previously failed therapy. Therefore, the FDA stated that the study failed to support the 60% remission rate claim as well as any conclusion that EFFEXOR XR is superior to other antidepressant treatments. In addition to the above claim, the FDA stated that other claims added to the misleading impression that patients who have failed previous antidepressant therapy can expect improvement when switching to EFFEXOR XR.

Claims from the PREVENT Study

The FDA objected to the claim, "In the PREVENT study, the probability of preventing a new episode of depression was 92% with EFFEXOR XR in maintenance year 2 vs. 55% with placebo." The FDA stated that the cited claim overstated the efficacy of EFFEXOR XR by implying that the general patient population suffering from major depressive disorder can expect a 92% probability of preventing a recurrent depressive episode after two years of treatment when this is not supported by substantial evidence.

The cited study for this claim was a randomized, multicenter, double-blind study (n=1096) comparing EFFEXOR XR with placebo. The study was designed to provide efficacy data regarding recurrence prevention with EFFEXOR XR after two years of maintenance treatment. It followed patients through 4 different time periods: a 10-week acute period, a 6-month continuation period, an initial 12-month maintenance period (maintenance year 1), and a second 12-month maintenance period (maintenance year 2). At the end of each period, patients were only considered eligible for inclusion in the next period if they were still responding to the drug. Patients dropped out of the study during each of the periods for different reasons (eg, lack of efficacy, adverse events). At the start of each maintenance period, the remaining patients who still showed a response to EFFEXOR XR were re-randomized to EFFEXOR XR or placebo. Because a high percentage of EFFEXOR XR patients were either re-randomized to placebo or were discontinued from the study before entering maintenance year 2 and because only patients who responded to EFFEXOR XR were selected to continue to the next phase of treatment, the FDA determined that the results of the study could not be extrapolated to the general patient population suffering from major depressive disorder.

Claim Regarding Clinical Experience and Number of Patients

The FDA objected to the claim, "More than 12 years of clinical experience and over 20 million patients treated with EFFEXOR/EFFEXOR XR." The claim of 20 million EFFEXOR/EFFEXOR XR patients was estimated from the number of U.S. prescriptions, average daily consumption, and average length of therapy. The FDA determined that this claim was misleading based on the referenced data because the calculations used did not reflect the number of "unique" patients. Because there are no unique patient-level data available for the entire 14-year period during which EFFEXOR/EFFEXOR XR has been on the U.S. market, the claim is no longer used in EFFEXOR XR promotional materials.

Please see brief summary of Prescribing Information on adjacent pages.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll free at 1-800-934-5556.

Suicidality and Antidepressant Drugs

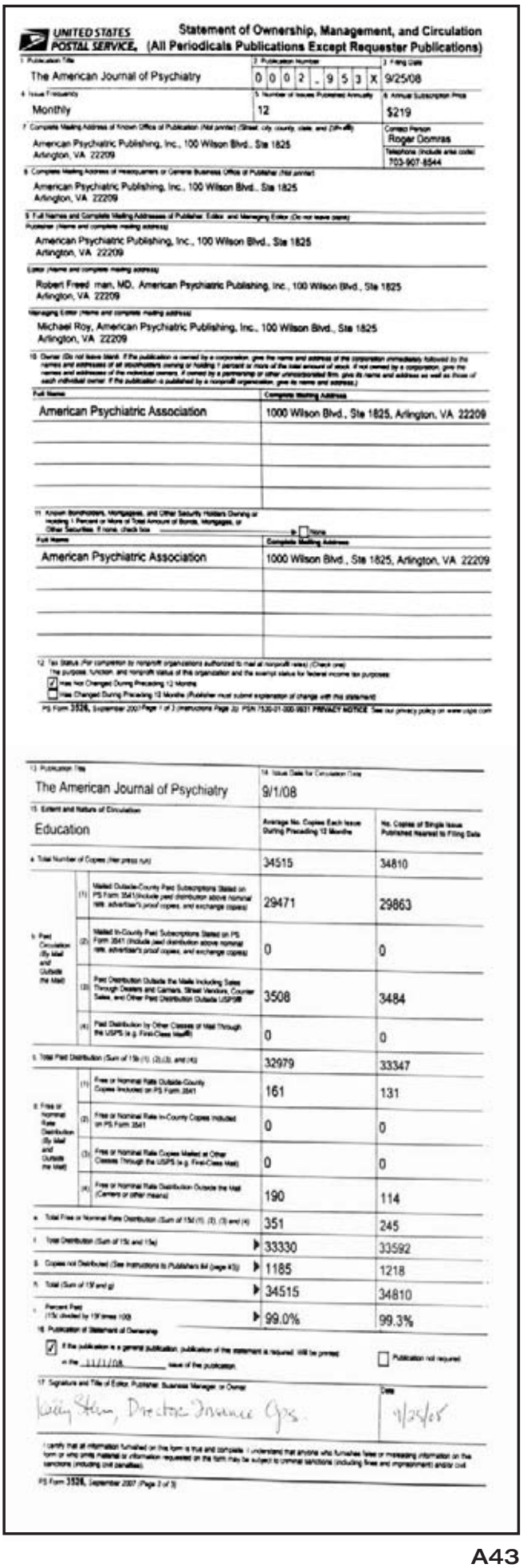
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: 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 trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) 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 reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 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 1,000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, 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. However, there is substantial evidence from placebo-controlled maintenance trials 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.** 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 and 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. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION). 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 health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone 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. Prior to initiating antidepressant treatment, patients with depressive symptoms should be 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. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **Elevations in Systolic and Diastolic Blood Pressure**—Across most indications, a dose-related increase in supine systolic and diastolic blood pressure was evident in EFFEXOR XR patients (for more information, see Table 4 of the full prescribing information). **Mydriasis**—Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients, in 3% of Generalized Anxiety Disorder (GAD) patients, and in 2% of Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 1% of SAD patients and 0.1% of PD patients. ***Changes in Weight***: ***Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In SAD trials of up to 6 months, 4% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both the MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height***: ***Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite***: ***Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (17%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.6% for up to 12 weeks in SAD studies; no patients discontinued for anorexia between week 12 and month 6. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during premarketing depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with SSRIs and SNRIs, including venlafaxine. Patients taking diuretics or who are otherwise volume depleted and elderly patients may be at greater risk. Discontinuation of Effexor XR should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. ***Seizures***: In all premarketing depression trials with Effexor immediate release, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: SSRIs and SNRIs, including EFFEXOR XR, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Bleeding events have ranged from ecchymoses, hematomas, epistaxes, and petechiae to life-threatening hemorrhages. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Interstitial Lung Disease and Eosinophilic Pneumonia***: These have been rarely reported. Consider the possibility of these events in venlafaxine patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation and should consider discontinuation of venlafaxine. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. It is recommended that the total daily dose be reduced by 50% in patients with mild to moderate hepatic impairment. In patients with cirrhosis, it may be necessary to reduce the dose even more than 50%. Individualization of dosing may be desirable. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide called "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk**: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents; and 4) about the concomitant use of Effexor XR and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Interfere with Hemostasis***: Epidemiological studies that have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Increased bleeding has been reported when SSRIs and SNRIs are coadministered with warfarin. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. A pharmacokinetic study with ketoconazole 100 mg b.i.d. with a single dose of venlafaxine 50 mg in extensive metabolizers (EM; n=14) and 25 mg in poor metabolizers (PM; n=6) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine (ODV) in most subjects following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of venlafaxine and ODV; therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and venlafaxine concomitantly. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Metoprolol***: In a PK study with 18 healthy males, metoprolol and venlafaxine were coadministered for 5 days. Plasma concentrations of metoprolol increased about 30%-40%. Plasma concentrations of metoprolol's active metabolite were unaltered. Metoprolol did not alter the PK of venlafaxine or ODV. Venlafaxine appeared to reduce the BP lowering effect of metoprolol in this study. Clinical relevance for hypertensive patients is unknown. Exercise caution when coadministering venlafaxine and metoprolol (see **WARNINGS—Sustained Hypertension**). ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome)**: Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis. **Pregnancy**—***Teratogenic Effects—Pregnancy Category C***: Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of

treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, 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**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Effexor XR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS: Hyponatremia**). **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 3 beats/min in SAD trials. (see **Sustained Hypertension** and **Elevations in Systolic and Diastolic Blood Pressure** sections of **WARNINGS**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR*** —N=7,212. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis, granuloma. **Cardiovascular system** - Frequent: migraine, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), postular hypotension, syncope; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia, thrombophlebitis. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipidemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, otitis media, parosmia, photophobia, taste loss; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis, visual field defect. **Urogenital system** - Frequent: albuminuria, urination impaired; Infrequent: amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; toxic epidermal necrolysis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

This brief summary is based on Effexor XR, Prescribing Information W10404C036 ET01, revised February 2008.

 231275-01



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PS Form 3526, September 2007 (Page 2 of 3)


Bipolar I Disorder
Manic or Mixed
It's hard enough being a teenager
It's even harder with
a serious mental illness
Schizophrenia

Acute and maintenance treatment of Manic and Mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients 10 to 17 years of age.

Help reveal the person within

ABILIFY is indicated for acute and maintenance treatment of Schizophrenia in adolescents 13 to 17 years of age.

Proven effective

Pediatric Bipolar I Disorder, Manic or Mixed (aged 10 to 17)

- Significant results demonstrated by mean change in Y-MRS Total Score at study endpoint (Week 4), in a randomized, placebo-controlled trial in pediatric patients with Bipolar I Disorder, Manic or Mixed[1]

Adolescent Schizophrenia (aged 13 to 17)

- Significant results demonstrated by mean change in PANSS™ Total Score at study endpoint (Week 6), in a randomized, placebo-controlled trial in adolescents with schizophrenia[2]
- High completion rate in large clinical trials of pediatric patients with Bipolar I Disorder, Manic or Mixed (N=296), and adolescents with Schizophrenia (N=302)[1,2]

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression (see Boxed WARNING).

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Pediatric patients (10 to 17 years) with bipolar mania: somnolence (23% vs 3%), extrapyramidal disorder (20% vs 3%), fatigue (11% vs 4%), nausea (11% vs 4%), akathisia (10% vs 2%), blurred vision (8% vs 0%), salivary hypersecretion (6% vs 0%), and dizziness (5% vs 1%)
- Adolescents (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs 5%), somnolence (16% vs 6%), and tremor (7% vs 2%)

The efficacy of ABILIFY for the maintenance treatment of Bipolar I Disorder or Schizophrenia in the pediatric population has not been evaluated. Maintenance efficacy can be extrapolated from adult data along with comparisons of ABILIFY pharmacokinetic parameters in adult and pediatric patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNINGS**, on next page.

Y-MRS: Young Mania Rating Scale.

PANSS™ (Positive and Negative Syndrome Scale) is a trademark of Multi-Health Systems, Inc.

ABILIFY® (aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

INDICATIONS

ABILIFY (aripiprazole) is indicated for:

- Acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients 10 to 17 years of age
- Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatrics 10 to 17 years of age
- Acute and maintenance treatment of Schizophrenia in adolescents 13 to 17 years of age

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindication – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

- **Cerebrovascular Adverse Events, Including Stroke** – Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Neuroleptic Malignant Syndrome (NMS)** – As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended
- **Tardive Dyskinesia (TD)** – The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely
- **Hyperglycemia and Diabetes Mellitus** – Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY

Orthostatic Hypotension – ABILIFY may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Seizures/Convulsions – As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment – Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Body Temperature Regulation – Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Suicide – The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Dysphagia – Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Pediatric patients (10 to 17 years) with Bipolar Mania: somnolence (23% vs 3%), extrapyramidal disorder (20% vs 3%), fatigue (11% vs 4%), nausea (11% vs 4%), akathisia (10% vs 2%), blurred vision (8% vs 0%), salivary hypersecretion (6% vs 0%), and dizziness (5% vs 1%)
- Pediatric patients (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs 5%), somnolence (16% vs 6%), and tremor (7% vs 2%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Please see FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, for ABILIFY on the adjacent pages.

References:

1. Data on file, Study 31-03-240. Otsuka America Pharmaceutical, Inc. Rockville, MD.
2. Data on file, Study 31-03-239. Otsuka America Pharmaceutical, Inc. Rockville, MD.

ABILIFY (aripiprazole)

TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

Bristol-Myers Squibb | Otsuka | Otsuka America Pharmaceutical, Inc.

570US08AB23903 October 2008 0308A-1465

Printed in USA ♻ Printed on recycled paper.

ABILIFY® (aripiprazole) Tablets
ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) Oral Solution

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see *Warnings and Precautions*).

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression (see *Warnings and Precautions*).

INDICATIONS AND USAGE: Schizophrenia - ABILIFY is indicated for acute and maintenance treatment of Schizophrenia in adolescents 13 to 17 years of age [see *Clinical Studies (14.1)* in Full Prescribing Information].

Bipolar Disorder - ABILIFY is indicated for acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in pediatric patients 10 to 17 years of age [see *Clinical Studies (14.2)* in Full Prescribing Information].

CONTRAINDICATIONS: Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis [see *Adverse Reactions*].

WARNINGS AND PRECAUTIONS: Use in Elderly Patients with Dementia-Related Psychosis - Increased Mortality: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*].

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis [see also *Boxed Warning*].

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy (placebo 2%, aripiprazole 5%), somnolence (including sedation) (placebo 3%, aripiprazole 8%), and incontinence (primarily urinary incontinence) (placebo 1%, aripiprazole 3%), excessive salivation (placebo 0%, aripiprazole 4%), and lightheadedness (placebo 1%, aripiprazole 4%). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration [see also *Boxed Warning*].

Clinical Worsening of Depression 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 trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with Major Depressive Disorder (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 reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 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 reported as: **Increases compared to placebo:** <18 (14 additional cases); 18-24 (5 additional cases); and **Decreases compared to placebo:** 25-64 (1 fewer case); ≥65 (6 fewer cases). No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, 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, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials 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 Major Depressive Disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either 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 Major Depressive Disorder 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. Prescriptions for ABILIFY should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 trials) 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 ABILIFY is not approved for use in treating depression in the pediatric population.

Neuroleptic Malignant Syndrome (NMS) - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia - A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY (aripiprazole) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus - Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY [see *Adverse Reactions*]. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with Schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Orthostatic Hypotension - Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of pediatric patients 10 to 17 years of age (n=399) on oral ABILIFY included orthostatic hypotension (1%, 0%), postural dizziness (0.3%, 0%), and syncope (0.3%, 0%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence); in pediatric oral aripiprazole-treated patients aged 10 to 17 years (0%, 0.5%). Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures/Convulsions - In short-term, placebo-controlled trials, seizures/convulsions occurred in 0.3% (1/399) of pediatric patients (10 to 17 years). As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment - ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in pediatric patients ages 10 to 17 (21%, 5%). Somnolence (including sedation) led to discontinuation in 1% (4/399) of pediatric patients (10 to 17 years) on oral ABILIFY in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation - Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see *Adverse Reactions*].

Suicide - The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive Disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose [see *Adverse Reactions*].

Dysphagia - Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see *Warnings and Precautions* and *Adverse Reactions*].

Use in Patients with Concomitant Illness - Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited [see *Use in Specific Populations*]. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies [see *Warnings and Precautions*].

ADVERSE REACTIONS: Overall Adverse Reactions Profile - The following are discussed in more detail in other sections of the labeling [see *Boxed Warning* and *Warnings and Precautions*]: Use in Elderly Patients with Dementia-Related Psychosis; Clinical Worsening of Depression and Suicide Risk; Neuroleptic Malignant Syndrome (NMS); Tardive Dyskinesia; Hyperglycemia and Diabetes Mellitus; Orthostatic Hypotension; Seizures/Convulsions; Potential for Cognitive and Motor Impairment; Body Temperature Regulation; Suicide; Dysphagia; Use in Patients with Concomitant Illness.

The most common adverse reactions in the pediatric clinical trials (≥10%) were somnolence, extrapyramidal disorder, headache, and nausea.

Aripiprazole has been evaluated for safety in 514 patients (10 to 17 years) who participated in multiple-dose, clinical trials in Schizophrenia or Bipolar Mania and who had approximately 205 patient-years of exposure to oral aripiprazole. A total of 270 pediatric patients were treated with oral aripiprazole for at least 180 days. 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 trials of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience - Pediatric Patients (13 to 17 years) with Schizophrenia: The following findings are based on one 6-week placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (13 to 17 years) was 8% and 2%, respectively.

Commonly Observed Adverse Reactions: Commonly observed adverse reactions associated with the use of aripiprazole in adolescent patients with Schizophrenia (≥5% incidence and at least twice the rate of placebo) were: extrapyramidal disorder, somnolence, and tremor.

Pediatric Patients (10 to 17 years) with Bipolar Mania: The following findings are based on one 4-week placebo-controlled trial in which oral aripiprazole was administered in doses of 10 mg/day or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (10 to 17 years) was 7% and 2%, respectively.

Commonly Observed Adverse Reactions: Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with Bipolar Mania (≥5% incidence and at least twice the rate of placebo for ABILIFY vs placebo (aripiprazole n=197, placebo n=97), respectively were: somnolence (23% vs. 3%), extrapyramidal disorder (20% vs. 3%), fatigue (11% vs. 4%), nausea (11% vs. 4%), akathisia (10% vs. 2%), blurred vision (8% vs. 0%), salivary hypersecretion (6% vs. 0%), and dizziness (5% vs. 1%).

Less Common Adverse Reactions in Pediatric Patients (10 to 17 years) with Schizophrenia or Bipolar Mania

The following treatment-emergent reactions reported in pediatric patients at an incidence of ≥1%, rounded to the nearest percent, with aripiprazole doses ≥2 mg/day, and at a greater incidence with aripiprazole than with placebo during short-term (up to 6 weeks in Schizophrenia and up to 4 weeks in Bipolar Mania), placebo-controlled trials (aripiprazole n=399, placebo n=197), respectively, were: somnolence (20%, 8%), extrapyramidal disorder (19%, 4%), headache (16%, 13%), nausea (10%, 5%), akathisia (9%, 4%), fatigue (7%, 3%), dizziness (5%, 2%), tremor (5%, 2%), blurred vision (5%, 0%), nasopharyngitis (4%, 3%), increased appetite (4%, 2%), salivary hypersecretion (4%, 1%), pyrexia (3%, 1%), weight increased (3%, 1%), diarrhea (3%, 0%), dry mouth (2%, 1%), rash (2%, 1%), stomach discomfort (2%, 1%), arthralgia (2%, 0%), dystonia (2%, 0%), dyskinesia (1%, 0%), orthostatic hypotension (1%, 0%), and sedation (1%, 0%).

Dose-Related Adverse Reactions - Schizophrenia: In the study of pediatric patients (13 to 17 years of age) with Schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%). ***Bipolar Mania:*** In the study of pediatric patients (10 to 17 years of age) with Bipolar Mania, four common adverse reactions had a possible dose response relationship at 4 weeks: extrapyramidal disorder (incidences were placebo, 3.1%; 10 mg, 12.2%; 30 mg, 27.3%); somnolence (incidences were placebo, 3.1%; 10 mg, 19.4%; 30 mg, 26.3%); akathisia (incidences were placebo, 2.1%; 10 mg, 8.2%; 30 mg, 11.1%); and salivary hypersecretion (incidences were placebo, 0%; 10 mg, 3.1%; 30 mg, 8.1%).

Extrapyramidal Symptoms: In the short-term, placebo-controlled trial of Schizophrenia in pediatric (13 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 5% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo. In the short-term, placebo-controlled trial in Bipolar Mania in pediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 10% vs. 2% for placebo. Objectively collected data from these trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the pediatric (13 to 17 years) Schizophrenia trial, the objectively collected data did

not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, -0.29).

In the pediatric (10 to 17 years) short-term Bipolar Mania trial, the Simpson Angus Rating Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.90; placebo, -0.05). Changes in the Barnes Akathesia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: A between group comparison for 4-week to 6-week, placebo-controlled trials in pediatric patients (10 to 17 years) revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis in pediatric patients.

Weight Gain: In a 6-week trial in pediatric patients (13 to 17 years) with Schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.13 kg vs. -0.03 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight (aripiprazole (6%) compared to placebo (1%)).

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions as defined in *Adverse Reactions* reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients, oral aripiprazole excluding those events already listed as adverse reactions in other parts of Full Prescribing Information, or those considered in *Warnings and Precautions*. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Pediatric Patients: Oral Administration - Most adverse events observed in the pooled database of 514 pediatric patients aged 10 to 17 years were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Gastrointestinal Disorders: ≥ *1/100 patients and* < *1/100 patients* - tongue dry, tongue spasm; *Investigations:* ≥ *1/100 patients* - blood insulin increased; *Nervous System Disorders:* ≥ *1/1000 patients and* < *1/100 patients* - sleep talking; *Skin and Subcutaneous Tissue Disorders:* ≥ *1/1000 patients and* < *1/100 patients* - hirsutism

Postmarketing Experience - The following adverse reactions have been identified during post-approval use of ABILIFY (aripiprazole). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

DRUG INTERACTIONS: Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol. Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY - Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole and Other CYP3A4 Inhibitors: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15 mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When ketoconazole is given concomitantly with aripiprazole, the aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions. Moderate inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Quinidine and Other CYP2D6 Inhibitors: Coadministration of a 10 mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when quinidine is given concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Carbamazepine and Other CYP3A4 Inducers: Coadministration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.

Potential for ABILIFY to Affect Other Drugs - Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. No effect of aripiprazole was seen on the pharmacokinetics of lithium or valproate.

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Drugs Having No Clinically Important Interactions with ABILIFY - Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500 mg/day-1500 mg/day) and aripiprazole (30 mg/day) were coadministered, at steady-state the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady-state there were no clinically significant changes in the C_{max} or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200 mg/day-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

Lamotrigine: Coadministration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients with Bipolar I Disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine.

Dextromethorphan: Aripiprazole (at doses of 10 mg/day to 30 mg/day for 14 days) had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 30 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Lorazepam: Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects (n=40; 35 males and 5 females; ages 19-45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone [see *Warnings and Precautions*].

Escitalopram: Coadministration of 10 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

Venlafaxine: Coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

Fluoxetine, Paroxetine, and Sertraline: A population pharmacokinetic analysis in patients with Major Depressive Disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 38%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

USE IN SPECIFIC POPULATIONS: In general, no dosage adjustment for ABILIFY (aripiprazole) is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function [see *Dosage and Administration (2.5)* in Full Prescribing Information].

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Labor and Delivery - The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers - Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use - Safety and effectiveness in pediatric patients with Major Depressive Disorder or agitation associated with Schizophrenia or Bipolar Mania have not been established.

Safety and effectiveness in pediatric patients with Schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [see *Indications and Usage, Dosage and Administration (2.1)* in Full Prescribing Information, *Adverse Reactions*, and *Clinical Studies (14.1)* in Full Prescribing Information]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Safety and effectiveness in pediatric patients with Bipolar Mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years [see *Indications and Usage, Dosage and Administration (2.2)* in Full Prescribing Information, *Adverse Reactions*, and *Clinical Studies (14.2)* in Full Prescribing Information]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between aripiprazole and lithium or valproate can be extrapolated from adult data, along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients. The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Geriatric Use - In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients [see also *Boxed Warning* and *Warnings and Precautions*].

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 299 (2%) were ≥75 years old. The majority (81%) of the 1073 patients were diagnosed with Dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole in Schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of aripiprazole injection in patients with agitation associated with Schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given as a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 52%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment - In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Gender - C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30% to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (20%) between men and women. No dosage adjustment is recommended based on gender.

Race - Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking - Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

DRUG ABUSE AND DEPENDENCE: ABILIFY is not a controlled substance.

Abuse and Dependence - Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Patients should be evaluated carefully for a history of drug abuse and closely observed for signs of ABILIFY misuse or abuse.

OVERDOSAGE: 76 cases of deliberate or accidental overdosage with oral aripiprazole alone or in combination with other substances were reported worldwide [44 cases with known outcome; 33 recovered without sequelae and one recovered with sequelae (rhythmic and feeling abnormal)]. Additionally, 10 of these cases were in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. The largest known acute ingestion was 1080 mg of oral aripiprazole (36 times maximum recommended daily dose) in a patient who fully recovered. Common adverse events (reported in at least 5% of all overdose cases) were vomiting, somnolence, and tremor. **For more information on symptoms of overdose, see Full Prescribing Information.**

Management of Overdosage: No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. **Charcoal:** In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%. **Hemodialysis:** Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

PATIENT COUNSELING INFORMATION: Information for Patients. Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY: [See Medication Guide (17.2) in Full Prescribing Information]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - Advise patients and caregivers of increased risk of death [see *Warnings and Precautions*].

Clinical Worsening of Depression and Suicide Risk - Alert families and caregivers of patients to monitor for the emergence of agitation, irritability, unusual changes in behavior, suicidality, and other symptoms as described in *Warnings and Precautions* and to report such symptoms immediately. Advise patients and their families and caregivers to read the Medication Guide and assist them in understanding its contents [see *Warnings and Precautions*].

Interference with Cognitive and Motor Performance - Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely [see *Warnings and Precautions*].

Pregnancy - Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY [see *Use in Specific Populations*].

Nursing - Patients should be advised not to breast-feed an infant if they are taking ABILIFY [see *Use in Specific Populations*].

Concomitant Medication - Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions [see *Drug Interactions*].

Alcohol - Patients should be advised to avoid alcohol while taking ABILIFY [see *Drug Interactions*].

Heat Exposure and Dehydration - Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions*].

Sugar Content - Patients should be advised that each mL of ABILIFY Oral Solution contains 400 mg of sucrose and 200 mg of fructose.

Phenylketonurics - Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT Orally Disintegrating Tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

Tablets manufactured by Otsuka Pharmaceutical Co. Ltd, Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Distributed and marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850 USA. Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. US Patent Nos. 5,006,528; 6,977,257; and 7,115,587.

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PSYCHIATRY
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CLINICAL NEUROLOGY FOR PSYCHIATRISTS
David Myland Kaufman, MD

This intensive three-day weekend course, offered for the 37th year, is designed for psychiatrists in practice and in residency as an update or board preparation. Focusing on essential topics, the course will use lectures, extensive syllabus, and the new edition of Clinical Neurology for Psychiatrists, David M. Kaufman (6th edition, Elsevier).

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The Westin Hotel at the Los Angeles Airport
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Friday, March 27 to Sunday, March 29, 2009
7:45 AM – 5:30 PM

NEW YORK
The Graduate Center
City University of New York (CUNY)
Friday, April 17 to Sunday, April 19, 2009
8:15 AM – 6:00 PM

PSYCHIATRY FOR PSYCHIATRISTS
Andrea J. Weiss, MD and David Myland Kaufman, MD

This two-day course will be a pre-test that will complement standard psychiatry review courses and complete the review in Clinical Neurology for Psychiatrists. In this course, an expert group of faculty who are experienced and well-informed about modern psychiatry and test-taking strategies will present essential information through a series of test-type questions utilizing audience response system keypads and using answers for discussions and explanations.

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The Westin Hotel at the Los Angeles Airport
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NEW YORK
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City University of New York (CUNY)
Monday, April 20 to Tuesday, April 21, 2009
8:15 AM – 6:00 PM

MAINTENANCE OF CERTIFICATION: THE RECERT COURSE
Dan Smuckler, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD

This intensive two-day course designed for psychiatrists will review the psychiatric information likely to appear on the recertification examination. It will cover current evidence-based treatments for psychiatric disorders, emphasizing clinical matters and advances in diagnosis and treatment. Presentation of the material will be in a mixed format, with both lecture and question and answer utilizing audience response system keypads.

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Clinical Neurology for Psychiatrists	☐ March 27-29 (Fri-Sun)	☐ April 17-19 (Fri-Sun)
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Maintenance of Certification	Not Available	☐ Jan. 30-31 (Fri-Sat)

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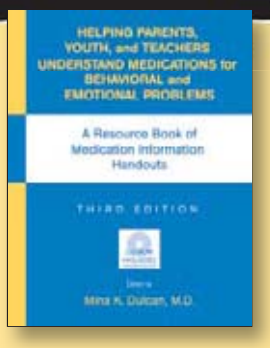

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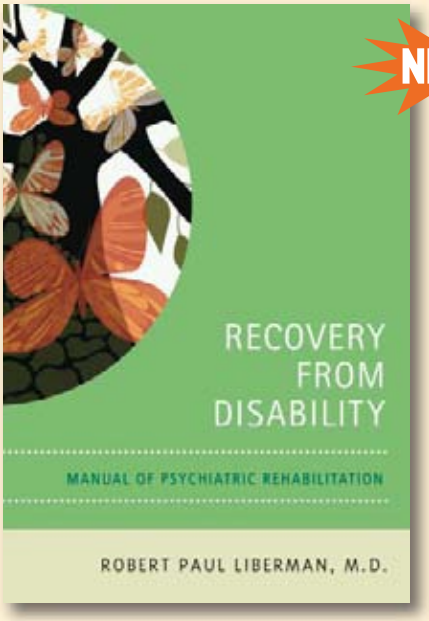
Recovery From Disability
Manual of Psychiatric Rehabilitation



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With its wealth of rich and immediately applicable treatment approaches, *Recovery From Disability* will help professionals equip mentally disabled patients to reach their personally relevant goals and progress on the road to recovery.

2008 • 628 pages • ISBN 978-1-58562-205-4 • Paperback • $65.00 • Item #62205

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Outpatient Psychiatry

Mayfield, KY
Outpatient Psychiatry

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Fax: 618-993-4148
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For program specific information, you may contact Dr. Lisa McCutchen, Director of Behavioral Medicine at 618-993-4161 or lisa.mccutchen@va.gov.

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Candidates should be Board Certified or Eligible in Psychiatry. The successful candidate will be appointed as a faculty member of the Dept of Psychiatry, College of Medicine. Rank and salary commensurate with qualifications and experience.

Please submit your CV and all contact information along with four letters of recommendation by 12/15/08 to:

Ena Casas
Department of Psychiatry
University of Illinois
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CHICAGO

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This physician would be expected to attend grand rounds and other departmental meetings as well. Excellent candidates will present a desire to be knowledgeable about the latest treatments of major psychiatric disorders. Opportunities for future research and/or other academic endeavors are possible, beginning with a focus on clinical study.

Rush University Medical Center is an academic medical center that encompasses a 618-bed hospital serving adults and children, the 58-bed Johnston R. Bowman Health Center and Rush University. Rush University is home to one of the first medical colleges in the Midwest and one of the nation's top-ranked nursing colleges, as well as graduate programs in allied health, health systems management and biomedical research. The Medical Center also offers more than 70 highly selective residency and fellowship programs in medical and surgical specialties and subspecialties.

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RUSH UNIVERSITY MEDICAL CENTER

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The Department of Psychiatry at the Indiana University School of Medicine is pleased to announce a new opening for a Full Professor (tenure or clinical track based on qualifications) to develop a comprehensive clinical, educational, and research program in Addiction Psychiatry and related disorders. The candidate should be Board Certified in Addiction Psychiatry and/or certified in Addiction Medicine.

This endowed position will provide direct support to the Indiana Department of Mental Health and Addiction in developing a Gambling Treatment Program; will provide clinical, education, and research support at Midtown Community Mental Health Center; and will also be head of the Addiction Psychiatry Fellowship Program within the Department of Psychiatry. The Midtown Community Mental Health Center addictions program includes adult outpatient services, intensive outpatient, outpatient detox, housing services for expectant mothers and newly parenting mothers, narcotics treatment program, and research programs under NIDA and SAMHSA.

The Department of Psychiatry has a broad research, clinical, and teaching mission and maintains both a clinical psychology internship and psychiatry residency program, in addition to training rotations for medical students. The department and the university place a high priority on creating a diverse learning environment and on supporting the professional development of ethnic minorities, women, and people with disabilities. Applications are encouraged from professionals of all ethnic backgrounds.

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Department of Psychiatry
Indiana University School of Medicine
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Kings County Hospital Center is the major teaching affiliate for SUNY Downstate Medical Center, NYC's only public medical school. The Behavioral Health Division has over 200 adult and child/adolescent inpatient beds, detoxification services, a Comprehensive Emergency Services Program, outpatient adult and child/adolescent mental health and chemical dependency services and an ACT and MCT Program.

As part of our continued commitment to the future of Psychiatry in Brooklyn, we continue to enhance, expand and reorganize our services as we prepare to move into a new $150M state-of-the-art building.

We seek a Board Certified Psychiatrist to serve as the Director of Behavioral Health Services. This position is accompanied by a SUNY academic appointment.

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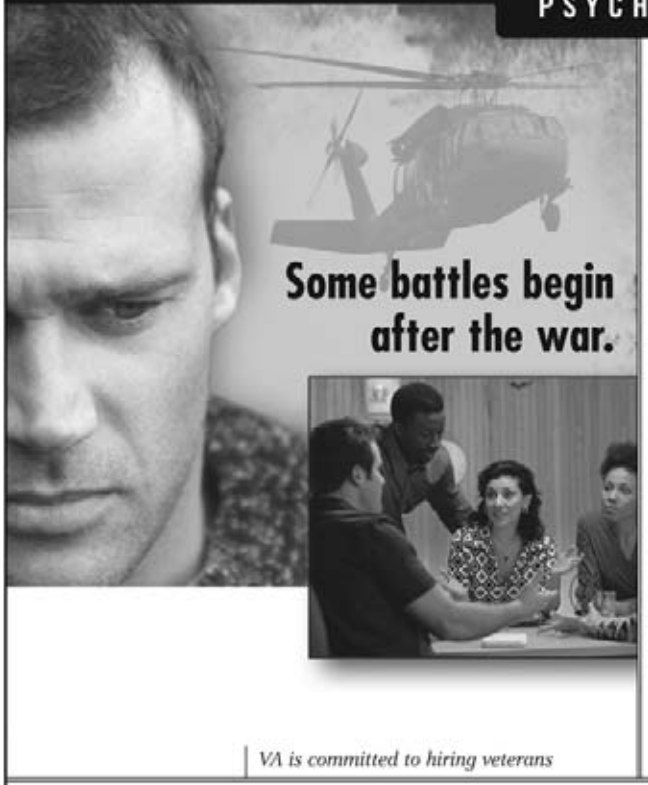
Please email your resume to Lois Sacks:
LSacks@ppasearch.com • Ph: **(914) 251-1000**

EOE

KINGS COUNTY HOSPITAL CENTER

PSYCHIATRISTS



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Scott & White and Texas A&M College of Medicine are seeking outstanding BC/BE individuals for the positions of Psychiatric Clinicians and Hospitalists within the Department of Mental Health Services at our main campus in Temple, TX. Candidates for this position should have strong credentials in clinical care and education, with inpatient psychiatric patient care experience. Academic responsibilities will include opportunities to mentor medical students and residents in basic psychiatric concepts, as well as delivering high quality health care to all population groups.

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Louis A. Johnson VA Healthcare System

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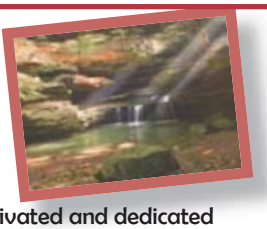
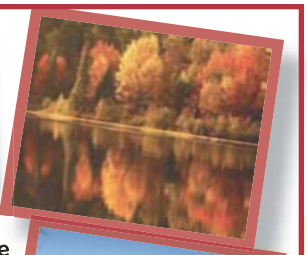
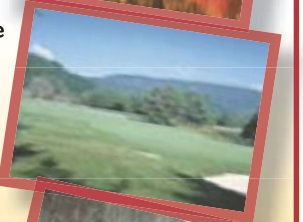

The Louis A. Johnson VA Healthcare System is actively recruiting highly motivated and dedicated professionals to join our Behavioral Medicine & Rehabilitation Service Team. Our progressive healthcare system includes the VA Medical Center in Clarksburg, WV, four Community Based Outpatient Clinics in Braxton, Tucker, Wood and Monongalia counties, plus a Community & Rural Healthcare Mobile Clinic. Successful candidates will join a team of highly skilled professionals who provide acute psychiatry and a broad scope of outpatient behavioral medicine services to veterans in north central West Virginia and surrounding counties of Ohio, Pennsylvania and Maryland.

We are currently recruiting for Psychiatrists and Psychologists for the Behavioral Medicine & Rehabilitation Service Team.

The Clarksburg, WV area offers the tranquility of rural living with ready access to metropolitan areas of Pittsburgh, PA, Washington, DC and Charleston, WV. The Louis A. Johnson VA Healthcare System is a healthcare leader in the community and offers an attractive recruitment and benefit package including:

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- Education Debt Reduction Fund
- Affiliation with the West Virginia University School of Medicine
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In addition, Recruitment & Relocation incentives may be offered. Please contact Dr. Glenn Snider, COS at (304) 623-3461 ext. 3206. For more information visit www.usajobs.gov

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Claudine Taub, RN, Dir. of Physician Recruitment
Phone: 715.498.3688
Fax: 715.342.7910
E-mail: mmgrecruitment@ministryhealth.org
ministryhealth.org/recruitment

*** Ministry Health Care is an Equal Opportunity Employer.

PSYCHIATRIST

The Department of Psychiatry at **The University of Texas Health Science Center at San Antonio (UTHSCSA)** seeks a Director of Adult Residency Training. The position is for a full-time board-certified academic psychiatrist at the Associate Professor or Professor level in the tenure or nontenure track.

The ideal candidate will have an emerging or established national reputation, show evidence of leadership and innovation in psychiatric residency training, have outstanding interpersonal skills, and sufficient administrative experience to manage and lead a large residency program.

The fully accredited program includes over 60 residents as well as ACGME approved fellowships in Geriatric and Forensic Psychiatry. Approval is being sought for a Psychosomatic Medicine Fellowship. This unique program includes residency slots from Wilford Hall Air Force Medical Center, University Hospital Health System, and the Audie Murphy Veterans Hospital.

Psychiatry has strong educational, research and clinical programs in an attractive, culturally rich city situated on the edge of the Texas Hill Country, with a pleasant climate, an excellent public school system and abundant recreational activities. Interested individuals should forward their curriculum vitae to:

Pedro L. Delgado, M.D.
Professor and Chairman, Department of Psychiatry
Mail Code 7792
The University of Texas Health Science Center at San Antonio 7703 Floyd Curl Drive
San Antonio TX 78229-3900
Phone: 210-567-5391
Fax: 210-567-6941

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ALEXANDRIA Strong clinical skills. Prefer experience in Geropsychiatry, Substance Abuse and/or PTSD. CV/Application to tammie.arnold@va.gov or Tammie Arnold, Psychiatry Service (116), P.O. Box 69004, Alexandria, LA 71306-9004. (318) 473-0010 ext 2696.

SHREVEPORT Prefer experience in Substance Abuse, PTSD. Contact Kay Cox at (318) 221-8411, ext 6772 or kay.cox@va.gov. Email or mail your CV to VAMC, HRMS (05) KC, 510 E. Stoner Ave, Shreveport, LA 71101.

FAYETTEVILLE, MT. VERNON, FORT SMITH Contact Laura Berg, HRMS, at laura.berg2@va.gov or (479) 443-4301, ext 5191.

MUSKOGEE, OK Contact Jason Cleveland, HRMS at 918-577-3800.

BC/BE ADULT PSYCHIATRIST

McLeod Health is seeking a Full-Time BC/BE Adult Psychiatrist for our Behavioral Health Psychiatric Center located in a beautiful rural setting in Darlington, SC, just minutes away from the main flagship hospital, McLeod Regional Medical Center in Florence, SC.

We have an extensive support staff for the hospital and ED consults and a twenty-four hour Access Center. Our state-of-the-art 23-bed crisis intervention in-patient facility was built and designed specifically for the needs of the psychiatric patient. We also provide out-patient therapy for patients in a private-practice setting.

We offer a competitive salary, comprehensive benefits and retirement package, paid professional liability insurance, CME allowance, relocation assistance, and sign-on bonus.

McLeod Regional Medical Center is a 453 bed, tertiary care, and teaching facility serving a primary market of 6 counties, and receiving tertiary referrals from 12 counties for a total population of 1 million people.

McLeod is leading the way for the nation in patient care by improving quality and safety. We are committed to developing patient-centered, evidence-based, physician-led quality health care in a not-for-profit hospital system that values each individual patient.

If you are interested in joining this nationally recognized hospital, please contact Janisyn McLaurin at 843-777-5169 or by email at jmclaurin@mcleodhealth.org.

STUDENT MENTAL HEALTH PSYCHIATRIC OPENING

CLINICAL ASSISTANT/ASSOCIATE PROFESSOR

Position# 00024621

The **University of Florida** Student Health Care Center and Department of Psychiatry at the University of Florida College of Medicine are seeking a Psychiatrist for a full time, non-tenure clinical position with primary responsibility in Student Mental Health.

The **University of Florida** is a large state university, which provides undergraduate, graduate, and professional education to an ethnically and culturally diverse population. Student Mental Health Services is comprised of the General Mental Health Clinic, Center for Sexual Assault/Abuse Recovery and Education, Eating Disorders Program, Alcohol and Substance Abuse Program, and Psychiatry Services.

The successful candidate would collaborate with a large multidisciplinary staff made up of psychologists, mental health counselors, psychiatrists, psychiatric ARNP's and other medical providers. In addition, this person will also have the opportunity to be involved in teaching and research through the Department of Psychiatry within the **University of Florida**, a major research university.

All applicants must have an MD/DO degree, must hold or be eligible for Florida Medical Licensure, be Board Certified or eligible for Board Certification and have a demonstrated record of clinical experience in assessment, brief treatment and psychopharmacological management. Faculty rank will be commensurate with experience. **Application deadline: November 21st.** Send CV and Letter of Interest to:

Sylvia Montesinos, M.D.
Search Committee Chairperson for Student Mental Health
P.O. Box 100256
University of Florida, Gainesville, FL 32610-0256
Equal Opportunity Institution

West Virginia University
Robert C. Byrd Health Sciences Center
Charleston Division

West Virginia University – Charleston Division, Department of Behavioral Medicine & Psychiatry is seeking a full-time academic BC general psychiatrist who is eligible for or has completed added qualifications in addiction psychiatry, either MD or DO, for evaluation and treatment of inpatient detoxification and substance abuse related consults in the hospital. Additionally, we are seeking two general psychiatrists. The candidates must also be eligible for licensure in the state of West Virginia. Recent inpatient experience is a must.

The opportunities involve teaching and supervisory responsibilities. Students include more than 20 residents in either a general psychiatry track or a med/psych track, 30 + medical students and three PhD psychology interns. Scholarly activity is strongly encouraged and supported.

The successful candidate will join a diverse and interdisciplinary faculty, including general psychiatrists, child and adolescent psychiatrists, geriatric psychiatrists, child psychology and neuropsychology.

West Virginia University – Charleston Division is the oldest regional medical campus in the United States. Over 100 clinical faculty provide training and educational oversight to more than 80 medical students and 140 residents. We are affiliated with Charleston Area Medical Center, a non-profit, 893-bed tertiary referral center. As Southern West Virginia's premier medical teaching facility, CAMC is home to one of the top heart programs in the United States; one of two kidney transplant centers in the state and one of the nation's busiest Level I trauma centers. CAMC has three Charleston locations: General Hospital, Memorial Hospital and Women and Children's Hospital.

Send letter of inquiry and CV to Martin J. Kommor, MD, WVU Department of Behavioral Medicine & Psychiatry, 3200 MacCorkle Ave., SE, Charleston, WV 25304, martin.kommor@camc.org or call **(304) 388-1010**.

Appointment will be at a level commensurate with experience and qualifications. The position will remain open until filled.

West Virginia University is an Affirmative Action/Equal Employment Opportunity Employer. Women and minorities are encouraged to apply.

Indiana University School of Medicine–
Eli Lilly and Co.
Psychopharmacology Research Fellowship

The Indiana University School of Medicine Department of Psychiatry in partnership with Eli Lilly and Co. is offering a one- to two-year research non-accredited fellowship in adult and/or child psychopharmacology. Candidates must have completed at least their PGY-III year to be eligible.

The fellowship will pair an investigator from IU with one from Lilly along a common diagnostic theme (mood or anxiety disorders, psychosis, dementia, childhood-onset disorders) or research approach (clinical trials, basic neuroscience, genetics, neuroimaging, etc.).

Fellows will spend at least 50% of their time at IU in outpatient, inpatient or laboratory research settings, and the remainder at the Lilly Corporate Research Facilities, located less than two miles away. The fellow will become proficient in state-of-the-art diagnostic/therapeutic approaches or laboratory/genetic/neuroimaging techniques.

Eligible applicants must be U.S. citizens or permanent residents and have completed an M.D. or comparable degree. One opening for the 2009-2010 academic year is available. Applications are encouraged from professionals of all ethnic backgrounds. Interested applicants should send a statement of interest, their curriculum vitae with a summary of relevant clinical/laboratory and academic experience, and the names of at least three references to:

David J. Posey, M.D.,
Associate Professor of Psychiatry
Riley Hospital for Children Room 4300
702 Barnhill Dr.
Indianapolis, IN 46202
dposey@iupui.edu

Applications will be accepted until the position is filled. The departmental website is located at http://psychiatry.medicine.iu.edu/. Indiana University is an EEO/AA Employer, M/F/D.

DEPARTMENT OF VETERANS AFFAIRS

The G.V. (Sonny) Montgomery VA Medical Center is recruiting for three full-time psychiatrists for the Mental Health Product Line. Duties may involve several aspects of general psychiatry, including inpatient, outpatient, consultative, or telemedicine psychiatry. The successful candidate must be board certified / board eligible in psychiatry.

Interest and experience in teaching and research are desirable. The incumbent should be eligible for a faculty appointment at the University of Mississippi School of Medicine, Department of Psychiatry. The G. V. (Sonny) Montgomery VA Medical Center, Mental Health Service is an integral part of the South Central VA Health Care Network, Mental Illness Research, Education and Clinical Center (MIRECC) with basic, clinical and health services project on schizophrenia, mood disorders, PTSD, substance abuse and dementia.

Our VA is a 163-bed acute care medical center with a 120-bed nursing home care unit, research and education facility, and outpatient clinics. We offer excellent benefits, such as, vacation/sick leave, health/life insurance coverage, and retirement package including a tax deferred savings plan.

VA Healthcare providers are entitled to immunity from medical malpractice claims as provided by the Federal Tort Claims Act. Applicant(s) selected for this position will be eligible to apply for an education loan reimbursement award under the provisions of the Education Debt Reduction Program (EDRP) subject to availability of EDRP funding.

Interested candidates should submit: Application for Physicians, Dentists, Podiatrists, and Chiropractors (VAF 10-2850) http://www.va.gov/vaforms/ and Declaration for Federal Employment (OF-306) http://www.opm.gov/forms/index.htm to:

Felicia Owens, HR Specialist
Human Resources Service (05P), VA Medical Center
1500 E. Woodrow Wilson Dr.
Jackson, MS 39216
Email: Felicia.Owens@va.gov
Phone : 601-364-1575

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Brief Summary—see package insert for full prescribing information.
ARICEPT® (Donepezil Hydrochloride Tablets)
ARICEPT® ODT (Donepezil Hydrochloride) Orally Disintegrating Tablets
INDICATIONS AND USAGE ARICEPT® is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild to moderate Alzheimer's Disease, as well as in patients with severe Alzheimer's Disease. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions** (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions) ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT® for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these drugs were observed. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations ($AUC_{0\text{-}24}$ and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m^2 basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m^2 basis). Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis). **Pregnancy** ***Pregnancy Category C:*** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **Geriatric Use** Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of the patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of the patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥65 years old and <65 years old. **ADVERSE REACTIONS** ***Mild To Moderate Alzheimer's Disease*** **Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1. **Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group (Placebo, 5 mg/day ARICEPT®, and 10 mg/day ARICEPT®, respectively); Patients Randomized (355, 350, 315); Event/% Discontinuing:** Nausea (1%, 1%, 3%); Diarrhea (0%, <1%, 3%); Vomiting (<1%, <1%, 2%). **Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®.** The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens. **Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks (No titration: Placebo [n=315], No titration: 5 mg/day [n=311], One week titration: 10 mg/day [n=315], Six week titration: 10 mg/day [n=269], respectively):** Nausea (6%, 5%, 19%, 6%); Diarrhea (5%, 8%, 15%, 9%); Insomnia (6%, 6%, 14%, 6%); Fatigue (3%, 4%, 8%, 3%); Vomiting (3%, 3%, 8%, 5%); Muscle cramps (2%, 6%, 8%, 3%); Anorexia (2%, 3%, 7%, 3%). **Adverse Events Reported in Controlled Trials** The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age. **Table 3. Adverse Events Reported in Controlled Clinical Trials in Mild to Moderate Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients (Body System/Adverse Event: Placebo [n=355], ARICEPT® [n=747], respectively): Percent of Patients with any Adverse Event: 72, 74. Body as a Whole:** Headache (9, 10); Pain, various locations (8, 9); Accident (6, 7); Fatigue (3, 5). **Cardiovascular System:** Syncope (1, 2). **Digestive System:** Nausea (6, 11); Diarrhea (5, 10); Vomiting (3, 5); Anorexia (2, 4). **Hemic and Lymphatic System:** Ecchymosis (3, 4). **Metabolic and Nutritional Systems:** Weight Decrease (1, 3). **Musculoskeletal System:** Muscle Cramps (2, 6); Arthritis (1, 2). **Nervous System:** Insomnia (6, 9); Dizziness (6, 8); Depression (<1, 3); Abnormal Dreams (0, 3); Somnolence (<1, 2). **Urogenital System:** Frequent Urination (1, 2). **Other Adverse Events Observed During Clinical Trials.** ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. ***Severe Alzheimer's Disease*** **Adverse Events Leading to Discontinuation:** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® patients were approximately 12% compared to 7% for placebo patients. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of ARICEPT® patients and at twice the incidence seen in placebo patients, were anorexia (2% vs 1% placebo), nausea (2% vs <1% placebo), diarrhea (2% vs 0% placebo), and urinary tract infection (2% vs 1% placebo). **Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®** The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving ARICEPT® and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and ecchymosis. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. **Adverse Events Reported in Controlled Trials** Table 4 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. **Table 4. Adverse Events Reported in Controlled Clinical Trials in Severe Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients (Body System/Adverse Event: Placebo [n=392], ARICEPT® [n=501], respectively): Percent of Patients with any Adverse Event: 73, 81. Body as a Whole:** Accident (12, 13); Infection (9, 11); Headache (3, 4); Pain (2, 3); Back Pain (2, 3); Fever (1, 2); Chest Pain (<1, 2). **Cardiovascular System:** Hypertension (2, 3); Hemorrhage (1, 2); Syncope (1, 2). **Digestive System:** Diarrhea (4, 10); Vomiting (4, 8); Anorexia (4, 8); Nausea (2, 6). **Hemic and Lymphatic System:** Ecchymosis (2, 5). **Metabolic and Nutritional Systems:** Creatine Phosphokinase Increased (1, 3); Dehydration (1, 2); Hyperlipemia (<1, 2). **Nervous System:** Insomnia (4, 5); Hostility (2, 3); Nervousness (2, 3); Hallucinations (1, 3); Somnolence (1, 2); Dizziness (1, 2); Depression (1, 2); Confusion (1, 2); Emotional Lability (1, 2); Personality Disorder (1, 2). **Skin and Appendages:** Eczema (2, 3). **Urogenital System:** Urinary Incontinence (1, 2). **Other Adverse Events Observed During Clinical Trials** ARICEPT® has been administered to over 600 patients with severe Alzheimer's Disease during clinical trials of at least 6 months duration, including 3 double blind placebo controlled trials, one of which had an open label extension. All adverse events occurring at least twice are included, except for those already listed in Table 4, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system using the COSTART dictionary and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Body as a Whole:** *Frequent:* abdominal pain, asthenia, fungal infection, flu syndrome; *Infrequent:* allergic reaction, cellulitis, malaise, sepsis, face edema, hernia. **Cardiovascular System:** *Frequent:* hypotension, bradycardia, ECG abnormal, heart failure; *Infrequent:* myocardial infarction, angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, cardiomegaly. **Digestive System:** *Frequent:* constipation, gastroenteritis, fecal incontinence, dyspepsia; *Infrequent:* gamma glutamyl transpeptidase increase, gastritis, dysphagia, periodontitis, stomach ulcer, periodontal abscess, flatulence, liver function tests abnormal, eructation, esophagitis, rectal hemorrhage. **Endocrine System:** *Infrequent:* diabetes mellitus. **Hemic and Lymphatic System:** *Frequent:* anemia; *Infrequent:* leukocytosis. **Metabolic and Nutritional Disorders:** *Frequent:* weight loss, peripheral edema, edema, lactic dehydrogenase increased, alkaline phosphatase increased; *Infrequent:* hypercholesteremia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B_{12} deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased, SGPT increased. **Musculoskeletal System:** *Frequent:* arthritis; *Infrequent:* arthrosis, bone fracture, arthralgia, leg cramps, osteoporosis, myalgia. **Nervous System:** *Frequent:* agitation, anxiety, tremor, convulsion, wandering, abnormal gait; *Infrequent:* apathy, vertigo, delusions, abnormal dreams, cerebrovascular accident, increased salivation, ataxia, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, extrapyramidal syndrome, grand mal convulsion, hemiplegia, hypertonia, hypokinesia. **Respiratory System:** *Frequent:* pharyngitis, pneumonia, cough increased, bronchitis; *Infrequent:* dyspnea, rhinitis, asthma. **Skin and Appendages:** *Frequent:* rash, skin ulcer, pruritus; *Infrequent:* psoriasis, skin discoloration, herpes zoster, dry skin, sweating, urticaria, vesiculobullous rash. **Special Senses:** *Infrequent:* conjunctivitis, glaucoma, abnormal vision, ear pain, lacrimation disorder. **Urogenital System:** *Frequent:* urinary tract infection, cystitis, hematuria, glycosuria; *Infrequent:* vaginitis, dysuria, urinary frequency, albuminuria. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature.

START AND STAY WITH ARICEPT®

Indicated for
MILD · MODERATE · SEVERE
Alzheimer's

Proven Efficacy for Patients...

- Improved behavior in mild to moderate AD[1]*
- Persistent treatment helped delay nursing home placement[2†]

and Benefits for Caregivers

- Caregivers of ARICEPT patients with mild to moderate AD experienced significantly less distress from patient behavioral problems[1]*

*The primary end point was the Neuropsychiatric Inventory (NPI); secondary measures included the Neuropsychiatric Inventory-Distress (NPI-D).
†As with observational follow-up studies of this type, results may be attributable to various factors. ARICEPT treatment was one such factor.

Important safety information

Cholinesterase inhibitors have the potential to increase gastric acid secretion. Patients at risk for developing ulcers, including those receiving concurrent NSAIDs, should be monitored closely for gastrointestinal bleeding.

In clinical trials, syncopal episodes have been reported (2% for ARICEPT versus 1% for placebo).

In clinical trials, the most common adverse events seen with ARICEPT were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, and ecchymosis. In studies, these were usually mild and transient.

Please see brief summary of prescribing information on adjacent page.

References: 1. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004;63:214-219. **2.** Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2003;51:937-944.

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