IN THE TREATMENT OF SCHIZOPHRENIA

It's hard to know **what patients *really* do** with their medication

Adhering to a medication regimen can often be a challenge for patients, including those with schizophrenia.

Studies suggest that 25% to 60% of patients may not take their antipsychotic medication as prescribed.[1-3]

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References: 1. Gilmer TP, Dolder CR, Lacro JP, et al. *Am J Psychiatry.* 2004;161(4):692-699. **2.** Becker MA, Young MS, Ochshorn E, Diamond RJ. *Adm Policy Ment Health & Ment Health Serv Res.* 2007;34(3):307-314. **3.** Velligan DI, Wang M, Diamond P, et al. *Psychiatr Serv.* 2007;58(9):1187-1192.

 September 2010 01PM10119

Cymbalta is indicated in adults for[1]:

- The treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in 4 short-term trials and 1 maintenance trial.
- The treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in 3 short-term trials and 1 maintenance trial.
- The management of diabetic peripheral neuropathic pain (DPNP).
- The management of fibromyalgia.

Reference: 1. Cymbalta full Prescribing Information.

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

Terms and Conditions

Reimbursement offered for up to 60 days of Cymbalta therapy to a maximum of $700. Prescriptions for more than 2 capsules per day are not eligible for reimbursement. Limit one reimbursement per person.

Offer void where prohibited by law. Valid only in the United States for US residents. Offer not valid for patients whose prescription claims for Cymbalta are reimbursed, in whole or in part, by (1) any governmental program, including, without limitation, Medicaid, Medicare, or any other federal or state program, such as Champus, the VA, TRICARE, or a state pharmaceutical assistance program, or (2) any third-party payer in the state of Massachusetts. By accepting this offer, patient agrees to notify his/her insurance carrier of reimbursement if required to do so by law or under the terms of coverage.

Additional exclusions may apply and this offer may be terminated, rescinded, revoked, or amended by Lilly USA, LLC, at any time without notice. Cymbalta® and the Cymbalta Logo are registered trademarks of Eli Lilly and Company.

Every Day, I think about what medication is the right choice for my patients.

Introducing the **Cymbalta Promise program**—a part of Every Day Connections. The Cymbalta Promise program is designed to help get the right patients on the right treatment—whether it's Cymbalta or not. If you and your patients who are new to Cymbalta are not satisfied, your patients may be reimbursed 100% of their out-of-pocket prescription costs for up to the first 60 days on Cymbalta. Ask your Cymbalta representative or visit cymbaltapromise.com to learn more. Restrictions apply. See full Terms and Conditions below. This program is not a guarantee of efficacy. It provides a trial period that may help patients and doctors assess the efficacy, safety, and tolerability of Cymbalta.

Every Day Connections

Important Safety Information About Cymbalta

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.

Contraindications

- 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.

  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 Important Safety Information, including Boxed Warning, above and on next page, and Brief Summary of full Prescribing Information on following pages.

Lilly

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl

Important Safety Information About Cymbalta *(Cont.)*

Contraindications *(Cont.)*

- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

Warnings and Precautions

- **Clinical Worsening and Suicide Risk**

  All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within 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 (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If discontinuing treatment, the medication should be tapered. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. 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.**

- 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.

- Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta 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 have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.

- The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. 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). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

- 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 abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

(cont.)

Important Safety Information About Cymbalta *(Cont.)*

Warnings and Precautions *(Cont.)*

- Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.
- In clinical trials across indications relative to placebo, treatment with Cymbalta was associated with mean increases of up to 2.3 mm Hg systolic and diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.
- Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.
- SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs.
- The effect that alterations in gastric motility may have on the stability of the enteric coating of Cymbalta is unknown. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., 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 (creatinine clearance <30 mL/min).
- As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases (up to 52 weeks) of the DPNP studies, an increase in HbA_{1c} in both the Cymbalta (0.5%) and the routine care groups (0.2%) was noted.
- Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

Use in Specific Populations

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child.

Adverse Events

- 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 (25% vs 9%), dry mouth (14% vs 6%), somnolence* (11% vs 3%), constipation* (11% vs 4%), decreased appetite* (8% vs 2%), and increased sweating (7% vs 2%).

  In addition to the adverse events listed above, DPNP trials also included: dizziness (13% vs 6%) and asthenia (5% vs 1%).

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

- In placebo-controlled clinical trials, the overall discontinuation rates due to adverse events were: **MDD:** 9% vs 5%; **GAD:** 15% vs 4%; **DPNP:** 14% vs 7%; **FM:** 20% vs 12%.

  The common adverse events reported as a reason for discontinuation and considered to be drug related were: **MDD:** nausea (1.3% vs 0.5%). **GAD:** nausea (3.7% vs 0.2%), vomiting (1.3% vs 0%), dizziness (1.0% vs 0.2%). **DPNP:** nausea (3.5% vs 0.4%), dizziness (1.6% vs 0.4%), somnolence (1.6% vs 0%), fatigue (1.1% vs 0%). **FM:** nausea (1.9% vs 0.7%), somnolence (1.5% vs 0%), fatigue (1.3% vs 0.2%).

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

Lilly

CYMBALTA®

(duloxetine hydrochloride) Delayed-Release Capsules for Oral use.

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). The efficacy of Cymbalta was established in four short-term trials and one maintenance trial in adults.

Generalized Anxiety Disorder—Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in three short-term trials and one maintenance trial in adults.

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 or Neuroleptic Malignant Syndrome (NMS)-like Reactions—The development of a potentially life-threatening serotonin syndrome or NMS-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. 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). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

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]*.

Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

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 7211 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% (2/2,489) of duloxetine-treated patients and 0.1% (1/1,625) 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% (3/9,445) of patients treated with duloxetine and 0.01% (1/6,770) 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. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

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% (209/2,327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1,460) 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

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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, restless legs syndrome, seizures upon treatment discontinuation, 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]*.

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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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Table 2: Change in Fasting Lipids

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=418	n=71	n=341	n=263	n=268
Total cholesterol	-8.5	-12.3	-9.4	-9.8	-3.8
Triglycerides	-15.7	-29.1	-6.2	-14.2	-3.1
Proportion of Patients with Shifts					
Total Cholesterol (≥ 240 mg/dL)	6.6% (23/350)	13.8% (8/58)	7.3% (21/287)	6.9% (15/216)	3.8% (9/238)
Triglycerides (≥ 200 mg/dL)	12.5% (39/312)	14.3% (7/49)	14.0% (37/264)	8.7% (17/196)	10.5% (22/209)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (n=238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 3. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 *[see Clinical Studies (14.1)]* change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

Table 3: Mean Change in Weight (kg) from Baseline

	Placebo (n=450)	LATUDA 20 mg/day (n=71)	LATUDA 40 mg/day (n=358)	LATUDA 80 mg/day (n=279)	LATUDA 120 mg/day (n=291)
All Patients	0.26	-0.15	0.67	1.14	0.68

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303) and -0.71 kg at week 52 (n=244).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was -0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 4).

Table 4: Median Change in Prolactin (ng/mL) from Baseline

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
All Patients	-0.6 (n=430)	-1.1 (n=70)	0.3 (n=351)	1.1 (n=259)	3.3 (n=284)
Females	-1.5 (n=102)	-0.7 (n=19)	-0.9 (n=99)	2.0 (n=78)	6.7 (n=70)
Males	-0.5 (n=328)	-1.2 (n=51)	0.5 (n=252)	0.9 (n=181)	3.1 (n=214)

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n=243).

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 considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology]*. 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, but the available evidence is too limited to be conclusive.

5.7 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood 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 LATUDA should be discontinued at the first sign of decline in WBC, in the 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 LATUDA and have their WBC followed until recovery.

5.8 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2% (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

LATUDA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

5.10 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

5.11 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 LATUDA for patients who will be experiencing conditions that 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 *[see Patient Counseling Information (17.9)]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13 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. LATUDA is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

7.2 Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{0\text{-}24}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{0\text{-}24}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{0\text{-}24}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully effected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately equal to the MRHD based on body surface area.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Labor and Delivery

The effect of LATUDA on labor and delivery in humans is unknown.

8.4 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

8.5 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.6 Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology]*. No dose adjustment is necessary in elderly patients.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.7 Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment (CL_{cr} ≥ 10 mL/min to < 50 mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92% and 54%, respectively and mean $AUC_{0\text{-}\infty}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

8.8 Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{0\text{-}\infty}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean C_{max} was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

8.9 Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean C_{max} of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

8.10 Race

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

8.11 Smoking Status

Based on in vitro studies utilizing human liver enzymes, LATUDA is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of LATUDA.

10. OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for 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 an acute overdose of LATUDA. Similarly the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

LATUDA (lurasidone HCl) Tablets
Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752

Revised: October 2010

LATUDA® (lurasidone HCl) Tablets

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 antipsychotic drugs are at an increased risk of death. Analyses of 17 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.

LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*

1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in four 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration]*.

4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.6)*].

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g. rifampin) [*see Drug Interactions (7.1)*].

5. WARNINGS AND PRECAUTIONS

5.1 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. LATUDA is not approved for the treatment of dementia-related psychosis [*see Boxed Warning*].

5.2 Cerebrovascular Adverse Reactions, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

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 creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. 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 NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive Dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can 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, LATUDA 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 LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

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. 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 suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

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 (e.g., 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.

Pooled data from short-term, placebo-controlled studies are presented in Table 1.

Table 1: Change in Fasting Glucose

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=438	n=71	n=352	n=270	n=283
Serum Glucose	-0.7	-0.6	2.5	-0.9	2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.6% (34/397)	11.7% (7/60)	14.3% (47/328)	10.0% (24/241)	10.0% (26/260)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236) and +1.2 mg/dL at week 52 (n=244).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 7: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (N=455) (%)	LATUDA 20 mg/day (N=71) (%)	LATUDA 40 mg/day (N=360) (%)	LATUDA 80 mg/day (N=282) (%)	LATUDA 120 mg/day (N=291) (%)
All EPS events	9	10	24	26	39
All EPS events, excluding Akathisia/ Restlessness	5	6	13	11	22
Akathisia	3	6	11	15	22
Dystonia*	1	0	4	5	7
Parkinsonism**	5	6	10	7	17
Restlessness	2	1	4	1	3

Note: Figures rounded to the nearest integer

*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

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.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events – 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

6.5 Laboratory Test Abnormalities and ECG Changes in Clinical Studies

Laboratory Test Abnormalities

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint [*see Warnings and Precautions (5.5)*]. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration [*see Warnings and Precautions (5.6)*]

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Population; Use in Specific Populations*].

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

6.6 Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 5 are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia;* ***Rare:*** *leukopenia, neutropenia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis, dysphagia*

General Disorders and Administrative Site Conditions: ***Rare:*** *Sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolic and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*

Renal and Urinary Disorders: ***infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Infrequent:*** *hypertension, orthostatic hypotension*

7 DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 8). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

Table 8: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered drug	Dose schedule		Effect on LATUDA pharmacokinetics		Recommendation
	Coadministered drug	LATUDA	C_{max}	AUC	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 5 days	10 mg single dose	6.9-times LATUDA alone	9-times LATUDA alone	Should not be coadministered with LATUDA
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-times LATUDA alone	2.2-times LATUDA alone	LATUDA dose should not exceed 40 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	1/7th of LATUDA alone	1/5th of LATUDA alone	Should not be coadministered with LATUDA
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	0.9-times LATUDA alone	1.1- times LATUDA alone	No LATUDA dose adjustment required.

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.7, 8.8)]*. LATUDA 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 (5.1, 5.8)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

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 studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies Experience

The following findings are based on the short-term placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n = 1004).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea, parkinsonism and agitation.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 5.

Table 5: Adverse Reaction in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=455)**	**All LATUDA (N=1004)**
Gastrointestinal Disorders		
Nausea	6	12
Vomiting	6	8
Dyspepsia	6	8
Salivary hypersecretion	<1	2
General Disorders and Administration Site Conditions		
Fatigue	3	4
Musculoskeletal and Connective Tissue Disorders		
Back Pain	3	4
Nervous System Disorders		
Somnolence*	10	22
Akathisia	3	15
Parkinsonism**	5	11
Dystonia***	1	5
Dizziness	3	5
Psychiatric Disorders		
Insomnia	7	8
Agitation	3	6
Anxiety	3	6
Restlessness	2	3

Note: Figures rounded to the nearest integer

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

***Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

6.3 Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 6).

Table 6: Dose-Related Adverse Events

	Percentage of Subjects Reporting Reaction				
Adverse Event Term	**Placebo (N=455) (%)**	**LATUDA 20 mg/day (N=71) (%)**	**LATUDA 40 mg/day (N=360) (%)**	**LATUDA 80 mg/day (N=282) (%)**	**LATUDA 120 mg/day (N=291) (%)**
Akathisia	3	6	11	15	22
Somnolence*	10	15	19	23	26

Note: Figures rounded to the nearest integer

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

6.4 Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 7).

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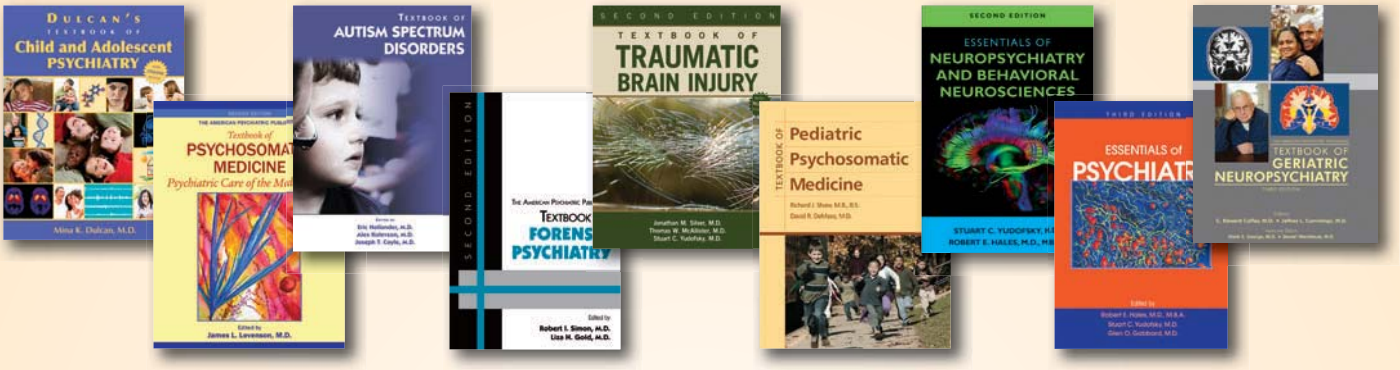

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INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration 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 is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients.

DOSAGE AND ADMINISTRATION

Schizophrenia GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment. Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials. *Maintenance Treatment*—While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving GEODON. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment. **Bipolar I Disorder** *Acute Treatment of Manic or Mixed Episodes*—Dose Selection: Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg to 80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg. *Maintenance Treatment* (as an adjunct to lithium or valproate)—Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg to 80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment. **Acute Treatment of Agitation in Schizophrenia** *Intramuscular Dosing*—The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied. If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible. Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended. Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously. Intramuscular Preparation for Administration GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration. Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Dosing in Special Populations** *Oral:* Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. GEODON is not approved for use in children or adolescents. *Intramuscular:* Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

CONTRAINDICATIONS

QT Prolongation Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone 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 ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone 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. Ziprasidone is also contraindicated with other 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**]. Ziprasidone 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 is not approved for the treatment of dementia-related psychosis (see BOXED WARNING).

QT Prolongation and Risk of Sudden Death Ziprasidone 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 ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**).

QT Prolongation in Clinical Trials A study directly comparing the QT/QT_c prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for ziprasidone 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 ziprasidone on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole

200 mg twice daily). In placebo-controlled trials, oral ziprasidone 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%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. **QT Prolongation and Torsade De Pointes** 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. Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) (see **ADVERSE REACTIONS**). A study evaluating the QT/QT_c prolonging effect of intramuscular ziprasidone, 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 ziprasidone (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 ziprasidone 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 ziprasidone 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 patients had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone 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, ziprasidone'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 ziprasidone 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. **Electrolyte Disturbances May Increase The Risk of QT Prolongation** It is recommended that patients being considered for ziprasidone 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 ziprasidone 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, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone 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** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment 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. If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical anti-psychotics. 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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia.

PRECAUTIONS

Leukopenia, Neutropenia, and Agranulocytosis In clinical trial and postmarketing experience, events of leukopenia/neutropenia and agranulocytosis (including fatal cases) have been reported temporally related to antipsychotic agents. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood 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 GEODON at the first sign of decline in WBC in the 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/mm3) should discontinue GEODON and have their WBC followed until recovery. **Rash** In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued. **Orthostatic Hypotension** Ziprasidone 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 the patients treated with ziprasidone. Ziprasidone 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). **Seizures** In clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone 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 ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **BOXED WARNING** and **Increased Mortality in Elderly Patients with Dementia-Related Psychosis in WARNINGS**). **Hyperprolactinemia** As with other drugs that antagonize dopamine D2 receptors, ziprasidone 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 reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone 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 ziprasidone therapy does not affect them adversely. **Priapism** One case of priapism was reported in the premarketing database. **Body Temperature Regulation** Although not reported with ziprasidone 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. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce overdose risk. **Patients With Concomitant Illnesses** Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited. Ziprasidone 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 ziprasidone, 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 assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients. **Laboratory Tests** Patients being considered for ziprasidone treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Discontinue ziprasidone in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**).

DRUG INTERACTIONS

(1) Ziprasidone should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents. (4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists. **Effect of Other Drugs on Ziprasidone** *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of ziprasidone. Ketoconazole, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect ziprasidone pharmacokinetics. Co-administration of 30 mL of Maalox® did not affect ziprasidone pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. **Effect of Ziprasidone on Other Drugs** *In vitro* studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement. Ziprasidone 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. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone 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 ziprasidone 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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Lifetime carcinogenicity studies were conducted with ziprasidone 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. Ziprasidone 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** in **PRECAUTIONS**). *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:* Ziprasidone increase 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/m2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m2 basis). The fertility of female rats was reduced.

USE IN SPECIFIC POPULATIONS

Pregnancy *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of ziprasidone on labor and delivery in humans is unknown. **Nursing Mothers** It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed. **Pediatric Use** The safety and effectiveness of ziprasidone in pediatric patients have not been established. **Geriatric Use** Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, 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 ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**). *Bipolar Mania:* Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone 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 of ≥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 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: 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 ziprasidone 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 (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo. **Dystonia** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. 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. Elevated risk of acute dystonia is observed in males and younger age groups. **Vital Sign Changes** Ziprasidone 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 ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. Weight gain was reported as an adverse event in 0.4% of both ziprasidone and placebo patients. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI. **ECG Changes** Ziprasidone is associated with an increase in the QT_c interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone 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 Ziprasidone in Schizophrenia** 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 adverse events are those occurring in fewer than 1/1000 patients. *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 trans-peptidase 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 Findings Observed in Trials of Intramuscular Ziprasidone** In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (≥5%) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence of ≥1% in Short-Term Fixed-Dose Intramuscular Trials** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of patients during acute therapy with intramuscular ziprasidone: *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. **Other Events Observed During Post-marketing Use** Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following—*Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see **WARNINGS**); *Digestive System Disorders:* Swollen Tongue; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Nervous System Disorders:* Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Ziprasidone is not a controlled substance.

OVERDOSAGE

In premarketing trials in over 5400 patients, accidental or intentional overdosage of oral ziprasidone 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 (200/95).

BIPOLAR I MAINTENANCE TREATMENT

GEODON + LITHIUM OR VALPROATE PROVEN SUPERIOR TO LITHIUM OR VALPROATE ALONE IN PREVENTING RELAPSE

GEODON®
(ziprasidone HCl) ***Capsules***

GEODON is indicated for acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder and for maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. For full symptoms and diagnostic criteria, see the *DSM-IV-TR®* (2000).

IMPORTANT SAFETY INFORMATION

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 a greater capacity to prolong the QT 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. Hypokalemia may increase the risk of QT prolongation and arrhythmia.

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.

The most common adverse events (≥5%) associated with GEODON in the bipolar maintenance study were tremor and insomnia.

Please see brief summary of prescribing information on adjacent page.

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