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Important Safety Information

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

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

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

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

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

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

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

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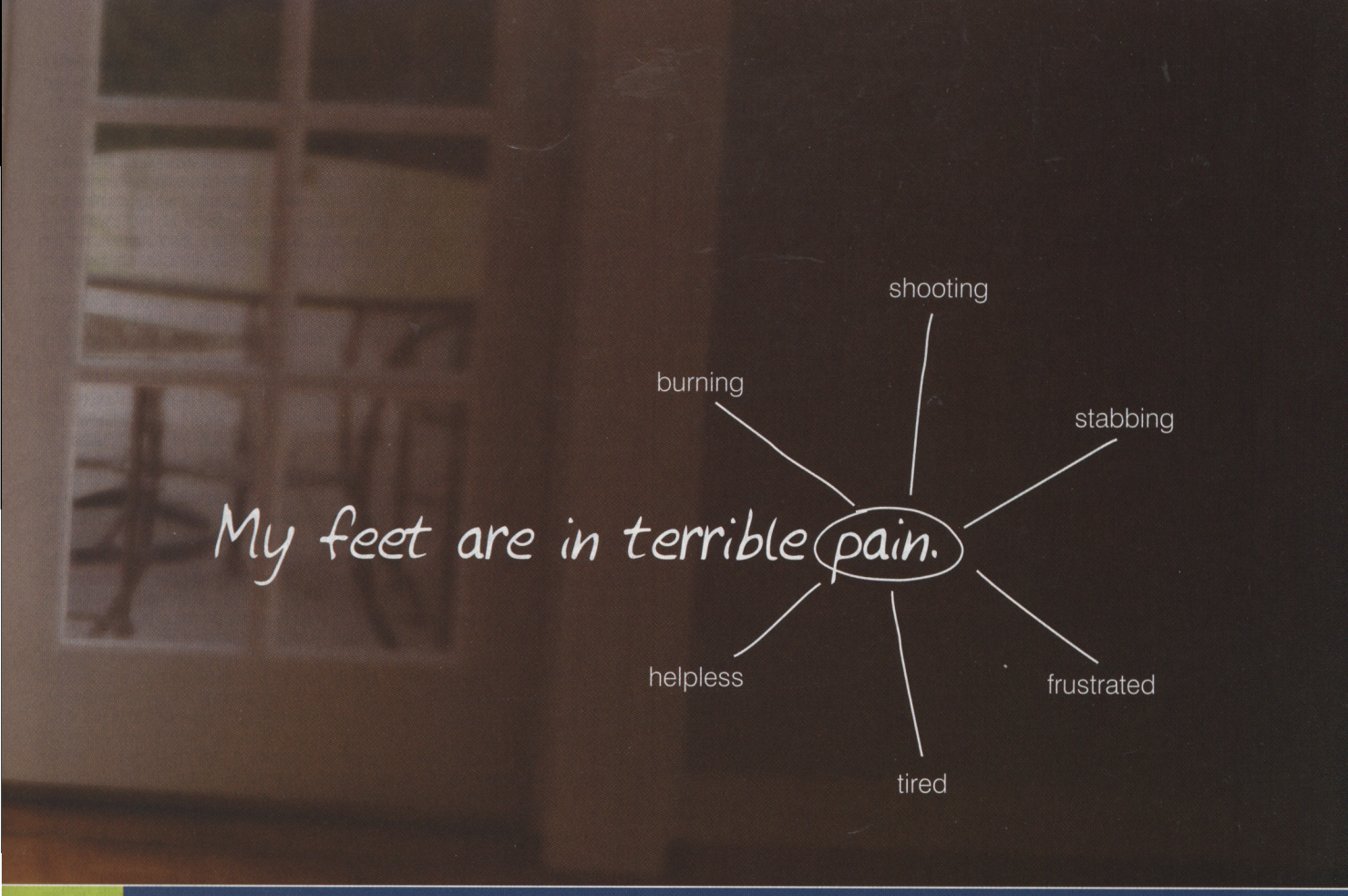

Manage the diabetic peripheral neuropathic pain (DPNP) symptoms your patients talk about, and those they don't. Many times, patients don't mention some of their symptoms because they don't realize they are related. That's where Cymbalta can help. Cymbalta provides relief from the dominant symptoms of DPNP and may help relieve underlying symptoms allowing you to treat patients more completely. To learn more about treating beyond the obvious, visit www.insidecymbalta.com

In pooled analysis and in individual studies, Cymbalta produced a significant separation ($P<.05$) from placebo on the weekly mean 24-hour average pain score at 12 weeks, the primary outcome of the study.[1]

Reference: 1. Data on file, Lilly Research Laboratories: CYM20051007B.

treat beyond the obvious

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

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

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

Coadministration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

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

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

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

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

The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=3563 vs 2178) were: nausea, dry mouth, somnolence,* constipation,* decreased appetite,* and increased sweating.

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding 3 MDD studies which did not have a placebo lead-in period or dose titration.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page.

Lilly

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CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

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).

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

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

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 abrupt 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—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (73/23,983) 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% (75/6871) of Cymbalta-treated patients compared to 0.3% (13/5036) 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. Postmarketing reports have described cases of 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. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

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

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

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

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

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

Cymbalta® (duloxetine hydrochloride) PV 5907 AMP

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Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal 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 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% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD 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 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) 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 BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

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

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

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

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

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%).

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%).

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=3563 Cymbalta; N=2178 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo were: nausea, dry mouth, diarrhea, dizziness*, insomnia (includes middle insomnia, early morning awakening, and initial insomnia), fatigue* (includes asthenia), somnolence* (includes hypersomnia and sedation), constipation*, 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.

The most commonly observed adverse reactions in duloxetine-treated patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

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

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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.

The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

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 DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; 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.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence ≤ placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

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 5 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 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 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.

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 BID, 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, 23,983 patients were treated with duloxetine. Of these, 6,702 took duloxetine for at least 6 months, and 3,006 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, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

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

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

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, andduloxetine $t_{1/2}$ 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 QD) with paroxetine (20 mg QD) 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 BID 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. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs 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]*.

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 BID).

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Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) 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 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) 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—Duloxetine's half-life 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.

Literature revised December 13, 2007

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EDITOR'S LETTER

CASE REPORT

ORIGINAL RESEARCH

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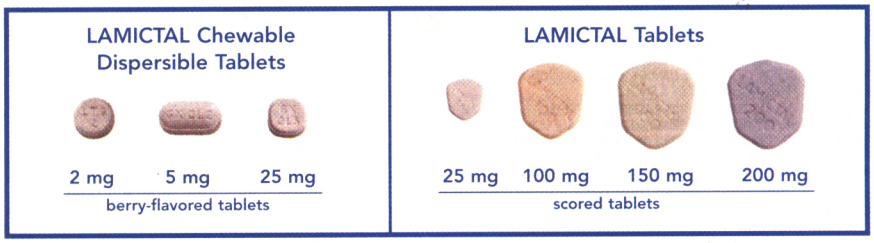
AVOID MEDICATION ERRORS

Medication errors have occurred involving LAMICTAL. To reduce the potential for medication errors, please write and say "LAMICTAL" clearly.

Patients may receive the wrong medication for several reasons, including medication errors, miscommunication between the physician's office and the pharmacy, or misread handwriting on a patient's prescription.



Initiating treatment with easy-to-follow Starter Kits may help reduce medication errors. Starter Kits are now available by prescription.

*For patients **NOT TAKING** carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or valproate*

*For patients **TAKING** valproate*

*For patients **TAKING** carbamazepine, phenytoin, phenobarbital, primidone, or rifampin and **NOT TAKING** valproate*

IMPORTANT NOTE:

Medication errors have occurred between LAMICTAL and other medications, most commonly Lamisil®,* lamivudine, Ludiomil®,* labetalol, and Lomotil®.* Patients who do not receive LAMICTAL would be inadequately treated and could experience serious consequences. Conversely, patients erroneously receiving LAMICTAL, especially high initial doses, would be unnecessarily subjected to a risk of serious side effects.

If you become aware of a prescription medication error involving these products, please contact GlaxoSmithKline at 1-888-825-5249; the USP Medication Errors Reporting Program at 1-800-233-7767; or the US Food and Drug Administration's MedWatch program by phone at 1-800-FDA-1088. You may also contact MedWatch by fax at 1-800-FDA-0178, via the Internet at www.fda.gov/medwatch, or by mail at: MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787.

At GlaxoSmithKline, we know that your priority is to ensure that every one of your patients receives optimal care. That is why we are committed to increasing awareness about the importance of preventing medication errors. Please remind patients to verify that they have received LAMICTAL.

*Lamisil (terbinafine HCl tablets) and Ludiomil (maprotiline HCl) are registered trademarks of Novartis Pharmaceuticals Corporation. Lomotil (diphenoxylate HCl, atropine sulfate) is a registered trademark of G.D. Searle LLC.

Please see Brief Summary of full Prescribing Information on adjacent pages, and please see the complete Prescribing Information for LAMICTAL at *www.LAMICTAL.com* for appropriate use of Starter Kits based on indications and concurrent medications.

gsk GlaxoSmithKline

LAMICTAL® (LAMOTRIGINE) TABLETS

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LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

BRIEF SUMMARY

The following is a brief summary only; see full prescribing information for complete product information.

SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8/1,000) IN PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3/1,000) IN ADULTS ON ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS INITIAL MONOTHERAPY AND 0.13% (1.3 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF 1,983 PEDIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMICTAL, THERE WAS 1 RASH-RELATED DEATH. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) COADMINISTRATION OF LAMICTAL WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

CONTRAINDICATIONS: LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL.

Serious Rash: ***Pediatrics:*** The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16/1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. It bears emphasis that LAMICTAL is only approved for use in patients below the age of 16 who have partial seizures or generalized seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS section of full prescribing information). There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6/482) experienced a serious rash compared to 0.6% (6/952) patients not taking valproate.

Adults: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11/3,348) of adult patients who received LAMICTAL in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1/1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2/1,538) of adult patients who received LAMICTAL as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate. Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with one or more of the following: fever, lymphadenopathy, facial swelling, hematologic, and hepatologic abnormalities. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered LAMICTAL in the absence of valproate were hospitalized. Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, 1 case was reported to be Stevens-Johnson–like.

Hypersensitivity Reactions: Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established. **Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.**

Acute Multiorgan Failure: Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2/3,796 adult patients and 4/2,435 pediatric patients who received LAMICTAL in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause.

Blood Dyscrasias: There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

Withdrawal Seizures: As with other AEDs (antiepileptic drugs), LAMICTAL should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see DOSAGE AND ADMINISTRATION section of full prescribing information).

PRECAUTIONS

Concomitant Use With Oral Contraceptives: Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine (see PRECAUTIONS: Drug Interactions). **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of LAMICTAL of full prescribing information).** During the week of inactive hormone preparation ("pill-free" week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse events consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

Dermatological Events (see BOX WARNING, WARNINGS): Serious rashes associated with hospitalization and discontinuation of LAMICTAL have been reported. It is not possible to predict reliably which rashes will prove to be serious or life threatening. Caution should be used when treating patients with a history of allergy or rash to other antiepileptic drugs, as the frequency of nonserious rash after treatment with LAMICTAL was approximately 3 times higher in these patients than in those without such history. It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash associated with prior treatment with LAMICTAL unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of LAMICTAL is affected by other concomitant medications (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism, and DOSAGE AND ADMINISTRATION sections of the full prescribing information).

Use in Patients With Epilepsy: ***Sudden Unexplained Death in Epilepsy (SUDEP):*** During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure). ***Status Epilepticus:*** In clinical trials, at a minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Use in Patients With Bipolar Disorder: ***Acute Treatment of Mood Episodes:*** Safety and effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

Children and Adolescents (less than 18 years of age): Treatment with antidepressants is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders. It is not known whether LAMICTAL is associated with a similar risk in this population (see PRECAUTIONS: Clinical Worsening and Suicide Risk Associated With Bipolar Disorder).

Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood disorders have not been established.

Clinical Worsening and Suicide Risk Associated With Bipolar Disorder: Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of which have been fatal (see OVERDOSAGE).

Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate (Dosage Reduction): Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence (see DOSAGE AND ADMINISTRATION section of full prescribing information).

Use in Patients With Concomitant Illness: Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or conditions that could affect metabolism or elimination of the drug, such as renal, hepatic, or cardiac functional impairment. The maintenance dose of LAMICTAL should generally be reduced for patients with significant renal impairment. Because there is limited experience with the use of LAMICTAL in patients with impaired liver function, the use in such patients may be associated with as yet unrecognized risks (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of full prescribing information).

Binding in the Eye and Other Melanin-Containing Tissues: Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues and may cause toxicity in these tissues after extended use. Accordingly, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Information for Patients: Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity may herald a serious medical event and that the patient should report any such occurrence to a physician immediately. In addition, the patient should notify his or her physician if worsening of seizure control occurs. Patients should be advised (1) that LAMICTAL may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression; (2) not to drive a car or operate other complex machinery until they have gained sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance; (3) of the possibility of blood dyscrasias and/or acute multiorgan failure and to contact their physician immediately if they experience any signs or symptoms of these conditions (see WARNINGS: Blood Dyscrasias and Acute Multiorgan Failure) (4) to notify their physicians if they become pregnant, intend to become pregnant, or intend to breast feed or are breast-feeding an infant during therapy; (5) to notify their physicians if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the "pill-free" week) may significantly increase lamotrigine plasma levels; (6) to notify their physician if they experience adverse events or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in combination with these medications; (7) to notify their physician if they stop taking LAMICTAL for any reason and not to resume LAMICTAL without consulting their physician. Patients should be informed of the availability of a patient information leaflet, and instructed to read the leaflet prior to taking LAMICTAL. See the PATIENT INFORMATION section of full prescribing information.

Laboratory Tests: The value of monitoring plasma concentrations of LAMICTAL has not been established. Because of the possible pharmacokinetic interactions between LAMICTAL and other drugs including AEDs, monitoring of the plasma levels of LAMICTAL and concomitant drugs may be indicated, particularly during dosing adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other drugs and whether or not dosage adjustments are necessary.

Drug Interactions: The net effects of drug interactions with LAMICTAL are summarized in Table 1 (see full prescribing information for additional information).

Oral Contraceptives: In 16 female volunteers, an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with a mean decrease in AUC of 52% and in C_{min} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive hormone preparation compared to trough lamotrigine concentrations at the end of the active hormone cycle. Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive hormone preparation ("pill-free" week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The increase in lamotrigine plasma levels will be greater if the dose of LAMICTAL is increased in the few days before or during the "pill-free" week. Increases in lamotrigine plasma levels could result in dose-dependent adverse effects (see PRECAUTIONS: Concomitant Use With Oral Contraceptives). In the same study, co-administration of LAMICTAL (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There was a mean decrease in the AUC and C_{min} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis. The effects of doses of LAMICTAL other than 300 mg/day have not been systematically evaluated in controlled clinical trials. The clinical significance of the observed hormonal changes on ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (e.g., break-through bleeding).

Dosage adjustments will be necessary for most women receiving estrogen-containing oral contraceptive preparations (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives of full prescribing information).

Other Hormonal Contraceptives or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

Table 3. Summary of Drug Interactions With LAMICTAL

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)‡	↔[1]	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide[#]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[1]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[#]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[**]	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

*From adjunctive clinical trials and volunteer studies. †Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies. ‡The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials and the effect may not be similar to that seen with the ethinylestradiol/levonorgestrel combinations. §Modest decrease in levonorgestrel (see PRECAUTIONS: Drug Interactions: Effect of LAMICTAL on Oral Contraceptives). ¶Not administered, but an active metabolite of carbamazepine. [1]Slight decrease, not expected to be clinically relevant. #Not administered, but an active metabolite of oxcarbazepine. **Slight increase not expected to be clinically relevant. ↔ = No significant effect. ? = Conflicting data.

Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above have not been systematically evaluated in combination with LAMICTAL. Since lamotrigine is metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of LAMICTAL may require adjustment based on clinical response.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m², respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded. Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone

marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities. No evidence of impairment of fertility was detected in rats given oral doses of lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg per day or 0.4 times the human dose on a mg/m^2 basis. The effect of lamotrigine on human fertility is unknown.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m^2 basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. *Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In* rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased. A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg per day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg per day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m^2 basis, respectively. Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m^2 basis. When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m^2 basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and *occurred between day 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity.* A no-observed-effect level (NOEL) could not be determined for this study. Although LAMICTAL was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: As with other antiepileptic drugs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary.

Pregnancy Exposure Registry: To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known**, and can obtain information by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll-free).

Labor and Delivery: The effect of LAMICTAL on labor and delivery in humans is unknown.

Use in Nursing Mothers: Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to LAMICTAL by this route are unknown, breast-feeding while taking LAMICTAL is not recommended.

Pediatric Use: LAMICTAL is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in patients above 2 years of age. Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not been established.

Geriatric Use: Clinical studies of LAMICTAL for epilepsy and in Bipolar Disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: (see BOX WARNING regarding the incidence of serious rash).

Epilepsy: Most Common Adverse Events in All Clinical Studies: ***Adjunctive Therapy in Adults With Epilepsy:*** The most commonly observed (≥5%) adverse experiences seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving CBZ with LAMICTAL than in patients receiving other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate (see WARNINGS). Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%). In a dose response study in adults, the rate of discontinuation of LAMICTAL for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose related.

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with the use of *LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were* vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5%) adverse experiences associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis. Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. In 339 patients age 2 to 16 years with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL and deterioration of seizure control for patients treated with placebo. Approximately 11.5% of the 1,081 pediatric patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy: Listed below are treatment-emergent signs and symptoms that occurred in ≥2% of adult patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to the patient's current AED therapy. Adverse events were usually mild to moderate in intensity. LAMICTAL was administered as adjunctive therapy to 711 patients; 419 patients received adjunctive placebo. Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category. **Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): Body as a whole:** Headache (29,19), flu syndrome (7.6), fever (6.4), abdominal pain (5,4), neck pain (2.1), reaction aggravated (seizure exacerbation) (2,1); **Digestive:** Nausea (19,10), vomiting (9,4), diarrhea (6,4), dyspepsia (5,2), constipation (4,3), tooth disorder (3,2), anorexia (2,1); **Musculoskeletal:** Arthralgia (2,0); **Nervous:** Dizziness (38,13), ataxia (22,6), somnolence (14,7), incoordination (6,2), insomnia (6,2), tremor (4,1), depression (4,3), anxiety (4,3), convulsion (3,1), irritability (3,2), speech disorder (3,0), concentration disturbance (2,1); **Respiratory:** Rhinitis (14,9), pharyngitis (10,9), cough increased (8,6); **Skin and appendages:** Rash (10,5), pruritus (3,2); **Special senses:** Diplopia (28,7), blurred vision (16,5), vision abnormality (3,1); **Urogenital (female patients only):** Dysmenorrhea (7,6), vaginitis (4,1), amenorrhea (2,1).

Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults With Epilepsy: In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL, some of the following drug-related adverse events were dose related. The adverse *events are listed by adverse experience followed by incidence in placebo first, LAMICTAL 300 mg dose second, and LAMICTAL 500 mg dose* third: ataxia (10,10,28), blurred vision (10,11,25), diplopia (8,24,49), dizziness (27,31,54), nausea (11,18,25), vomiting (4,11,18). Other events that occurred in more than 1% of patients but equally or more frequently in the placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia, paresthesia, respiratory disorder, and urinary tract infection. The overall adverse experience profile for LAMICTAL was similar between females and males, and was independent of age. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. Generally, females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse experiences than males. The only adverse experience for which the reports on LAMICTAL were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was little difference between females and males in the rates of discontinuation of LAMICTAL for individual adverse experiences.

Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures: Listed below are treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group. 43 patients *received monotherapy with LAMICTAL up to 500 mg/day; 44 received low-dose VPA monotherapy at 1,000 mg/day.* Patients in these studies were converted to LAMICTAL or VPA monotherapy from adjunctive therapy with CBZ or PHT. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category. **Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial (Events in at least 5% of patients treated with LAMICTAL and numerically more frequent than in the valproate group are listed by body system with the incidence for LAMICTAL followed by valproate): Body as a whole:** Pain (5,0), infection (5,2), chest pain (5,2); **Digestive:** Vomiting (9,0), dyspepsia (7,2), nausea (7,2); **Metabolic and nutritional:** Weight decrease (5,2); **Nervous:** Coordination abnormality (7,0), dizziness (7,0), anxiety (5,0), insomnia (5,2); **Respiratory:** Rhinitis (7,2); **Urogenital (female patients only):** Dysmenorrhea (5,0).

Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving LAMICTAL and numerically more frequent than placebo were: ***Body as a Whole:*** Asthenia, fever. ***Digestive:*** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer. ***Metabolic and Nutritional:*** Peripheral edema. ***Nervous System:*** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation. ***Respiratory:*** Epistaxis, bronchitis, dyspnea. ***Skin and Appendages:*** Contact dermatitis, dry skin, sweating. ***Special Senses:*** Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy: Listed below are adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to 15 mg/kg per day or a maximum of 750 mg per day. LAMICTAL was administered as adjunctive therapy to 168 patients; 171 patients received adjunctive placebo. **Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): Body as a whole:** Infection (20,17), fever (15,14), accidental injury (14,12), abdominal pain (10,5), asthenia (8,4), flu syndrome (7,6), pain (5,4), facial edema (2,1), photosensitivity (2,0); **Cardiovascular:** Hemorrhage (2,1); **Digestive:** Vomiting (20,16), diarrhea (11,9), nausea (10,2), constipation (4,2), dyspepsia (2,1), tooth disorder (2,1); **Hemic and lymphatic:** Lymphadenopathy (2,1); **Metabolic and nutritional:** Edema (2,0); **Nervous system:** Somnolence (17,15), dizziness (14,4), ataxia (11,3), tremor (10,1), emotional lability (4,2), gait abnormality (4,2), thinking abnormality (3,2), convulsions (2,1), nervousness (2,1), vertigo (2,1); **Respiratory:** Pharyngitis (14,11), bronchitis (7,5), increased cough (7,6), sinusitis (2,1), bronchospasm (2,1); **Skin:** Rash (14,12), eczema (2,1), pruritus (2,1); **Special senses:** Diplopia (5,1), blurred vision (4,1), ear disorder (2,1), visual abnormality (2,0); **Urogenital:** Urinary tract infection (male and female patients) (3,0), penis disorder (2,0).

Bipolar Disorder:

During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse experience. The adverse events which most commonly led to discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse events (2%).

Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance Treatment of Bipolar I Disorder: Listed below are treatment-emergent signs and symptoms that occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in 2 double-blind, placebo-controlled trials of 18 months' duration and were numerically more frequent than in the placebo group. LAMICTAL was administered as monotherapy to 227 patients; 190 patients received placebo. Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category. **Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder (Events in at least 5% of patients treated with LAMICTAL monotherapy and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo.) General:** Back pain (8,6); fatigue (8,5), abdominal pain (6,3); **Digestive:** Nausea (14,11), constipation (5,2), vomiting (5,2); **Nervous System:** Insomnia (10,6), somnolence (9,7), xerostomia (dry mouth) (6,4); **Respiratory:** Rhinitis (7,4), exacerbation of cough (5,3), pharyngitis (5,4); **Skin:** Rash (non serious) (7,5).

Adverse events that occurred in at least 5% of patients and were numerically more common during the dose escalation phase of LAMICTAL in these trials (when patients may have been receiving concomitant psychotropic medications) compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

Other events that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia. Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients receiving LAMICTAL and numerically more frequent than placebo were: ***General:*** Fever, neck pain. ***Cardiovascular:*** Migraine. ***Digestive:*** Flatulence. ***Metabolic and Nutritional:*** Weight gain, edema. ***Musculoskeletal:*** Arthralgia, myalgia. ***Nervous System:*** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia. ***Respiratory:*** Sinusitis. ***Urogenital:*** Urinary frequency.

Adverse Events Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients after abruptly terminating LAMICTAL therapy. In clinical trials in patients with Bipolar Disorder, 2 *patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have* contributed to the occurrence of seizures in these bipolar patients (see DOSAGE AND ADMINISTRATION section of full prescribing information).

Mania/Hypomania/Mixed Episodes: During the double-blind, placebo-controlled clinical trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months, the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined, adverse events of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803).

The overall adverse event profile for LAMICTAL was similar between females and males, between elderly and nonelderly patients, and among racial groups.

Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders: LAMICTAL has been administered to 6,694 individuals for whom complete adverse event data were captured during all clinical trials, only some of which were placebo controlled. All reported events are included except those already listed above, those too general to be informative, and those not reasonably associated with the use of the drug. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1,000 patients; *rare* events occurred in ≤1/1,000 patients.

Body as a Whole: Infrequent: Allergic reaction, chills, halitosis, and malaise. ***Rare:*** Abdomen enlarged, abscess, and suicide/suicide attempt. ***Cardiovascular System: Infrequent:*** Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. ***Rare:*** Angina pectoris, atrial fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction. ***Dermatological: Infrequent:*** Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. ***Rare:*** Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, seborrhea, Stevens-Johnson Syndrome, and vesiculobullous rash. ***Digestive System: Infrequent:*** Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. ***Rare:*** Gastrointestinal hemorrhage, *glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and* tongue edema. ***Endocrine System: Rare:*** Goiter and hypothyroidism. ***Hematologic and Lymphatic System: Infrequent:*** Ecchymosis and leukopenia. ***Rare:*** Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia. ***Metabolic and Nutritional Disorders: Infrequent:*** Aspartate transaminase increased. ***Rare:*** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia. ***Musculoskeletal System: Infrequent:*** Arthritis, leg cramps, myasthenia, and twitching. ***Rare:*** Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture. ***Nervous System: Frequent:*** Confusion and paresthesia. ***Infrequent:*** Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation. ***Rare:*** Cerebellar syndrome, cerebrovascular accident, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, *hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.* ***Respiratory System: Infrequent:*** Yawn. ***Rare:*** Hiccup and hyperventilation. ***Special Senses: Frequent:*** Amblyopia. ***Infrequent:*** Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. ***Rare:*** Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect. ***Urogenital System: Infrequent:*** Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormality. ***Rare:*** Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and vaginal moniliasis.

Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation. ***Blood and Lymphatic:*** Agranulocytosis, aplastic anemia, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia. ***Gastrointestinal:*** Esophagitis. ***Hepatobiliary Tract and Pancreas:*** Pancreatitis. ***Immunologic:*** Lupus-like reaction, vasculitis. ***Lower Respiratory:*** Apnea. ***Musculoskeletal:*** Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions. ***Neurology:*** Exacerbation of parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics. ***Non-site Specific:*** Hypersensitivity reaction, multiorgan failure, progressive immunosuppression.

DRUG ABUSE AND DEPENDENCE: The abuse and dependence potential of LAMICTAL have not been evaluated in human studies.

OVERDOSAGE: Human Overdose Experience: Overdoses involving quantities up to 15 g have been reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

Management of Overdose: There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL PHARMACOLOGY section of full prescribing information). It is uncertain *whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of* lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL.

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we can't wait

Because I don't want to lose my son to the voices again.

The voices in his head are back.
I can't bear to see him like this.

He was doing so well on his own.
This will ruin everything.
It could send him back to the hospital.

We're fighting to get
things back under control.
But we need help now.

ZYPREXA®
Olanzapine

For resources to help you help your patients with schizophrenia, visit **www.ToolsForTheFight.com**

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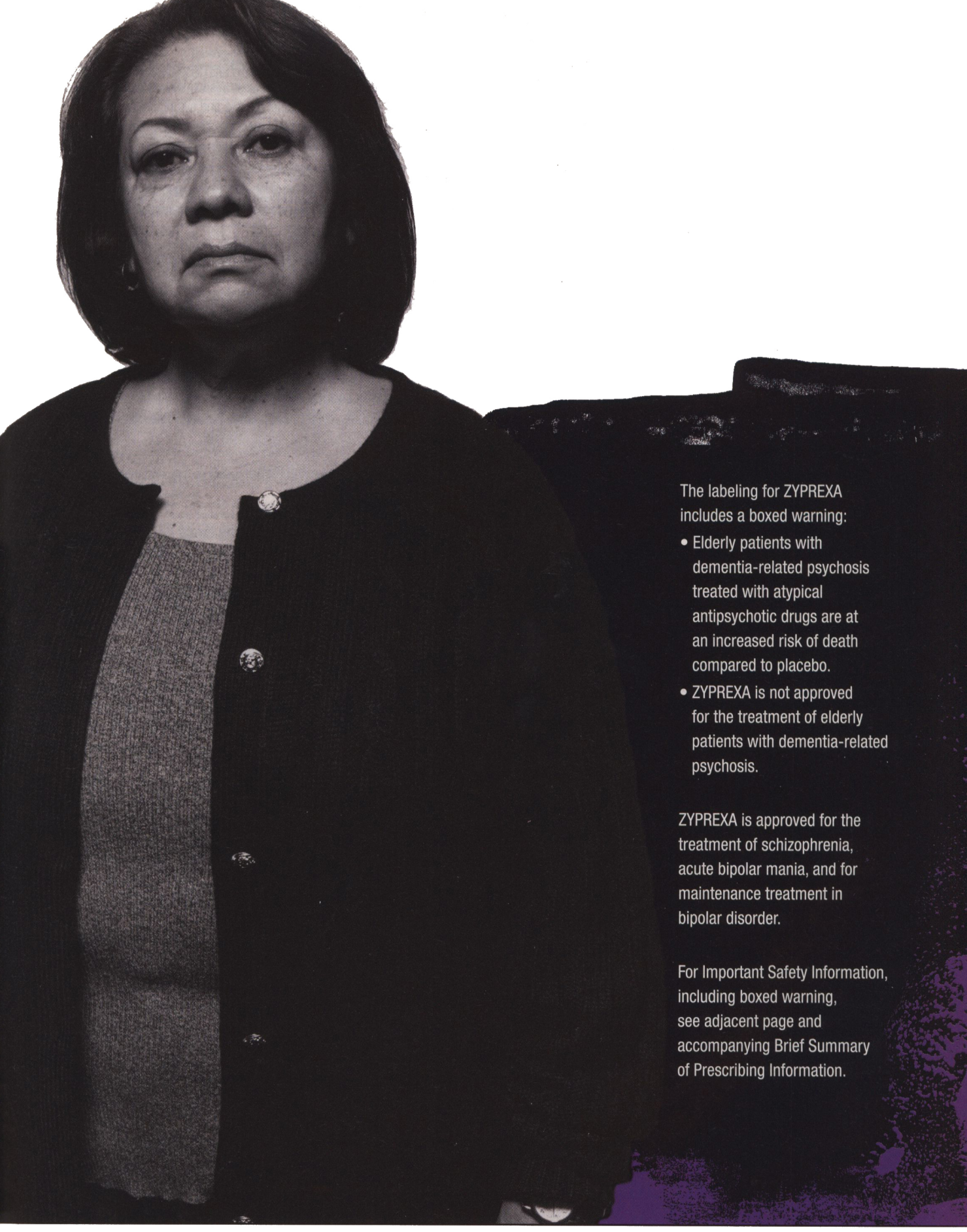

The labeling for ZYPREXA includes a boxed warning:

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

ZYPREXA is approved for the treatment of schizophrenia, acute bipolar mania, and for maintenance treatment in bipolar disorder.

For Important Safety Information, including boxed warning, see adjacent page and accompanying Brief Summary of Prescribing Information.

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Important Safety Information for ZYPREXA® (Olanzapine)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking olanzapine should be monitored regularly for worsening of glucose control. Persons with risk factors for diabetes who are starting on atypical antipsychotics should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Hyperlipidemia—Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Significant, and sometimes very high, elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Weight gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. 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.

Tardive dyskinesia (TD)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Other potentially serious adverse events include orthostatic hypotension, seizures, hyperprolactinemia, transaminase elevations, and dysphagia.

The safety and efficacy of ZYPREXA have not been established in patients under the age of 18 years.

Medication dispensing and prescribing errors have occurred between ZYPREXA® (olanzapine) and Zyrtec® (cetirizine HCl). These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder. To reduce the potential for dispensing errors, please write ZYPREXA clearly.

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials was somnolence (26% vs 15%). Other common events were dizziness (11% vs 4%), weight gain (6% vs 1%), personality disorder (COSTART term for nonaggressive objectionable behavior; 8% vs 4%), constipation (9% vs 3%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials was somnolence (35% vs 13%). Other common events were dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).

For complete safety profile, see the full Prescribing Information.

Lilly

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ZYPREXA® (Olanzapine Tablets)
ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)
ZYPREXA® IntraMuscular (Olanzapine for Injection)
Brief Summary: Please consult package insert for complete prescribing information.

WARNING

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

INDICATIONS AND USAGE: ZYPREXA and ZYPREXA Zydis are indicated for short- and long-term treatment of schizophrenia, for acute manic and mixed episodes of bipolar I disorder, and for maintenance treatment in bipolar disorder. The use of ZYPREXA for extended periods should be periodically re-evaluated as to the long-term usefulness of the drug for the individual patient. ZYPREXA IntraMuscular is indicated for treatment of agitation associated with schizophrenia and bipolar I mania.

CONTRAINDICATIONS: Known hypersensitivity to olanzapine.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients (3.5%) was significantly greater than placebo-treated patients (1.5%).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia—Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. See the package insert for information on glycemic changes in adult and adolescent populations.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes who are starting treatment with atypicals should have fasting blood glucose (FBG) testing at baseline and periodically during treatment. Any patient treated with atypicals should be monitored for symptoms of hyperglycemia. Patients who develop symptoms of hyperglycemia during treatment with atypicals should undergo FBG testing.

Hyperlipidemia—Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use. See the package insert for information on lipid changes in adult and adolescent populations.

Weight Gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight. See the package insert for information on weight change in adult and adolescent populations.

Neuroleptic Malignant Syndrome (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See the package insert for information on management of NMS. Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences have been reported.

Tardive Dyskinesia (TD)—Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. If signs and symptoms of TD appear, consider drug discontinuation.

PRECAUTIONS: Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness; tachycardia; and in some patients, syncope. Hypotension, bradycardia with/without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. Incidence of syncope was 0.6%, 15/2500 with oral olanzapine in phase 2-3 trials and 0.3%, 2/722 with intramuscular olanzapine for injection in clinical trials. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of events may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. Patients should remain recumbent if drowsy or dizzy after injection with intramuscular olanzapine for injection until examination has indicated they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put them at increased medical risk. Caution is necessary in patients receiving treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or CNS depression (*see* Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is not recommended. If such combination treatment is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients, regardless of causality. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyperprolactinemia—Like other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels; a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro. However, neither clinical nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is inconclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal) were observed in 2% (6/243) of patients exposed to olanzapine compared to no (0/115) placebo patients. None of these patients experienced jaundice. Among about 2400 patients with baseline SGPT ≤90 IU/L, 2% (50/2381) had asymptomatic SGPT elevations to >200 IU/L. Most were transient changes that tended to normalize while olanzapine treatment was continued. Among 2500 patients in oral olanzapine trials, about 1% (23/2500) discontinued treatment due to transaminase increases. Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period. Exercise caution in patients who have signs and symptoms of hepatic impairment; preexisting conditions associated with limited hepatic functional reserve; or concomitant treatment with potentially hepatotoxic drugs (*see* Laboratory Tests, below).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported, dose-related adverse event in premarketing trials (olanzapine 26% vs placebo 15%). Somnolence led to discontinuation in 0.4% (9/2500) of patients in the oral premarketing database.

Body Temperature Regulation—Use appropriate care when prescribing olanzapine for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management.

Use in Patients with Concomitant Illnesses—Olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In 5 placebo-controlled studies in elderly patients with dementia-related psychosis (n=1184), these treatment-emergent adverse events were reported with olanzapine at an incidence of ≥2% and significantly greater than with placebo: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, visual hallucinations. Discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat this patient population, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

Because of the risk of orthostatic hypotension with olanzapine, use caution in cardiac patients (*see* Hemodynamic Effects).

Information for Patients—Patients should be advised of the potential risk of hyperglycemia-related adverse events and monitored regularly for worsening of glucose control. Patients should be counseled that olanzapine is associated with weight gain and should have their weight monitored regularly. See the package insert for additional information to discuss with patients taking olanzapine.

Laboratory Tests—*Periodic assessment of transaminases is recommended in patients with significant* hepatic disease.

Drug Interactions—Use caution when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzymes (e.g., omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. A dosage adjustment may need to be considered with specific drugs.

Activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) nor warfarin (20 mg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the Cmax of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small in comparison to the overall variability between individuals, and dose modification is not routinely recommended. Fluvoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients receiving fluvoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Olanzapine is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Single doses of olanzapine did not affect the pharmacokinetics of imipramine/desipramine or warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam/N-desmethyldiazepam, lithium, ethanol, or biperiden. However, coadministration of either diazepam or ethanol potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites. Co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (*see* Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility—The incidence of liver hemangiomas and hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human daily oral dose (MHDOD) but not in another study at 2-5 times the MHDOD (mg/m^2 basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/d group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice and rats given olanzapine at 0.5 and 2 times the MHDOD respectively (mg/m^2 basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown. No evidence of mutagenic potential for olanzapine has been found.

In rats, fertility (females) and mating performance (males and females) were affected at doses 1.5-11 times the MHDOD (mg/m^2 basis). Diestrous was prolonged and estrous delayed at 0.6 times the MHDOD (mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Pregnancy Category C—There are no adequate and well-controlled studies in pregnant women. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery, Nursing Mothers—Parturition in rats was not affected by olanzapine; its effect on labor and delivery in humans is unknown. In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal dose. It is recommended that women receiving olanzapine should not breast-feed.

Use in Pediatric and Geriatric Patients—The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In premarketing clinical trials in patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger adult patients. Studies in elderly patients with dementia-related psychosis have suggested there may be a different tolerability profile in these patients. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat these patients, vigilance should be exercised. Consider a lower starting dose for any geriatric patient in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine (*see* BOX WARNING, WARNINGS, *and* PRECAUTIONS).

ADVERSE REACTIONS: The following findings are based on a clinical trial database consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection, including patients with schizophrenia, bipolar mania, or Alzheimer's disease (oral olanzapine trials) and patients with agitation associated with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia (intramuscular olanzapine for injection trials). See the package insert for details on these trials. Certain portions of the discussion below relating to dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation; however, this information is also generally applicable to bipolar mania and agitation.

Associated with Discontinuation—Overall there was no difference in discontinuations due to adverse events in placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania monotherapy, 2% vs 2%; bipolar mania cotherapy, 11% [olanzapine plus lithium or valproate] vs 2% [lithium or valproate alone]); or in placebo-controlled intramuscular olanzapine for injection trials (olanzapine for injection, 0.4%; placebo 0%). Discontinuations in oral schizophrenia trials due to increases in SGPT were considered to be drug related (olanzapine 2% vs placebo 0%; *see* PRECAUTIONS).

Commonly Observed Adverse Events—In 6-week, placebo-controlled, premarketing schizophrenia trials, the most common treatment-emergent adverse events associated with oral olanzapine (incidence ≥5% and olanzapine incidence at least twice that for placebo) were: postural hypotension, constipation, weight gain, dizziness, personality disorder (COSTART term for nonaggressive objectionable behavior), and akathisia. In 3- and 4-week placebo-controlled bipolar mania monotherapy trials, the most common treatment-emergent adverse events associated with oral olanzapine were: asthenia, dry mouth, constipation, dyspepsia, increased appetite, somnolence, dizziness, and tremor. In short-term bipolar mania combination therapy trials, the most common treatment-emergent adverse events observed with olanzapine plus lithium or valproate were dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, and paresthesia. In 24-hour placebo-controlled trials of intramuscular olanzapine for injection for agitation associated with schizophrenia or bipolar mania, somnolence was the one adverse event observed at an incidence of ≥5% and at least twice that for placebo (olanzapine for injection 6%, placebo 3%).

Adverse Events with an Incidence ≥2% in Oral Monotherapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥2.5 mg/d), and at a greater incidence with olanzapine than with placebo in short-term placebo-controlled trials (olanzapine N=532, placebo N=294): ***Body as a Whole***—accidental injury, asthenia, fever, back pain, chest pain; ***Cardiovascular***—postural hypotension, tachycardia, hypertension; ***Digestive***—dry mouth, constipation, dyspepsia, vomiting, increased appetite; ***Hemic and Lymphatic***—ecchymosis; ***Metabolic and Nutritional***—weight gain, peripheral edema; ***Musculoskeletal***—extremity pain (other than joint), joint pain; ***Nervous System***—somnolence, insomnia, dizziness, abnormal gait, tremor, akathisia, hypertonia, articulation impairment; ***Respiratory***—rhinitis, cough increased, pharyngitis; ***Special Senses***—amblyopia; ***Urogenital***—urinary incontinence, urinary tract infection.

Adverse Events with an Incidence ≥2% in Oral Combination Therapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥5 mg/d) plus lithium or valproate (N=229), and at a greater incidence than with placebo plus lithium or valproate (N=115) in short-term placebo-controlled

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trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; **Digestive**—dry mouth, increased appetite, thirst, constipation, increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

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

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