CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

APPROVED LABELING

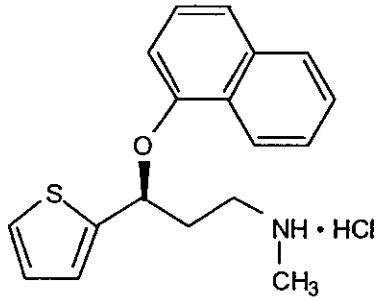
A3.0 NL 3600 AMP

CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

DESCRIPTION

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$, which



corresponds to a molecular weight of 333.88. The structural formula is:

Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the exact mechanisms of the antidepressant and central pain inhibitory action of duloxetine in humans are unknown, the antidepressant and pain inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2.

Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Special Populations

Gender — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the C_{max}, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary (*see* DOSAGE AND ADMINISTRATION).

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.

Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end-stage renal disease receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. For this reason, Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl] <30 mL/min) (*see* DOSAGE AND ADMINISTRATION). Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with any hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — When duloxetine was co-administered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n=14) the AUC was increased over 5-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6 — 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 of duloxetine (*see* PRECAUTIONS, Drug Interactions).

Studies with Benzodiazepines

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.

Potential for Duloxetine to Affect Other Drugs

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. Although duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg BID). Duloxetine is thus unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6 (*see* PRECAUTIONS). Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and that have a narrow therapeutic index should be approached with caution (*see* PRECAUTIONS, Drug Interactions).

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.

Studies with Benzodiazepines

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

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

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 events.

CLINICAL STUDIES

Major Depressive Disorder

The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any additional benefit.

In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Diabetic Peripheral Neuropathic Pain

The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathy for at least 6 months. Study 1 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to Cymbalta. Patients recorded their pain daily in a diary.

Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

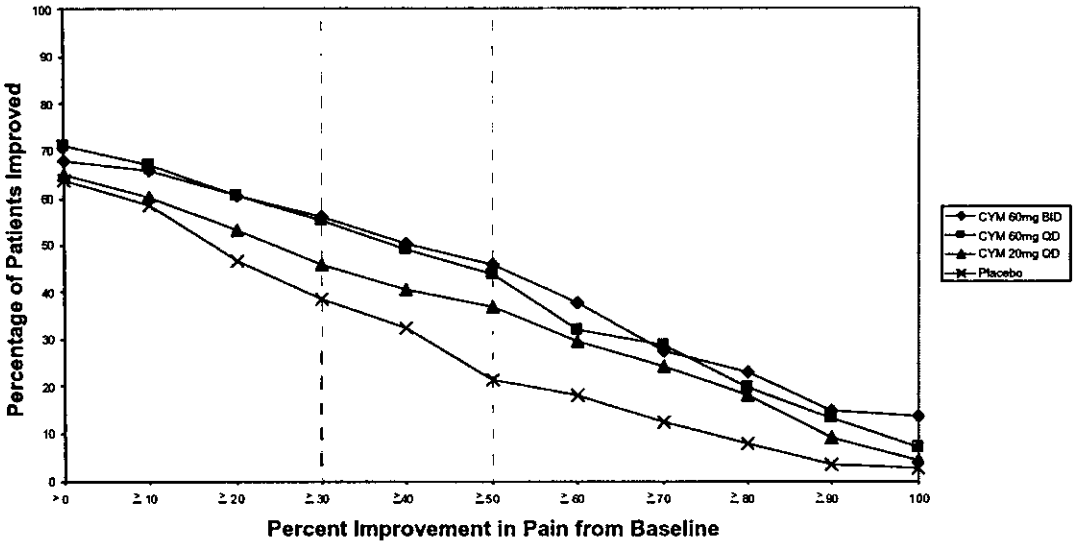


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

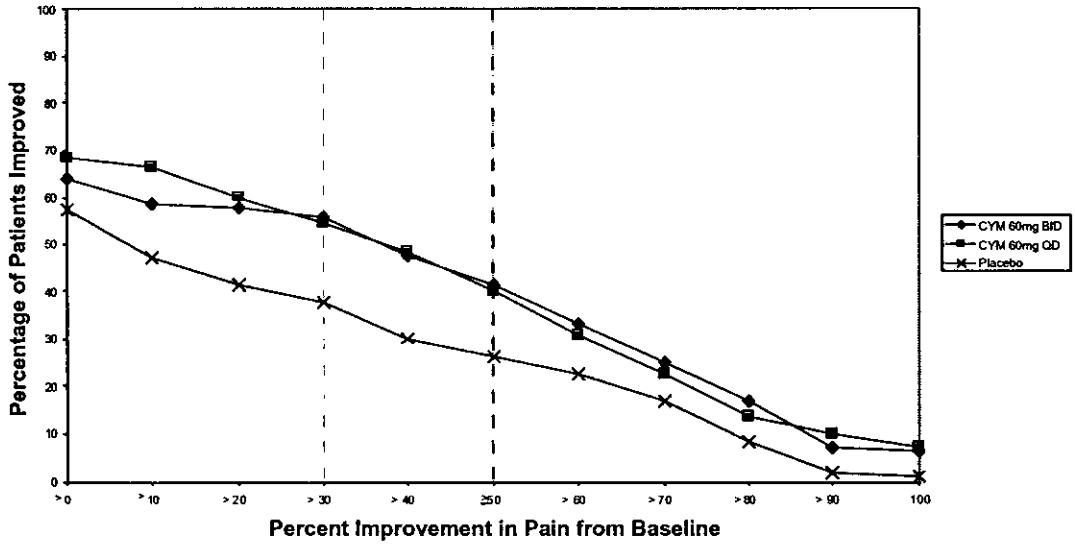


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

INDICATIONS AND USAGE

Major Depressive Disorder

Cymbalta is indicated for the treatment of major depressive disorder (MDD).

The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see* CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Diabetic Peripheral Neuropathic Pain

Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (*see* CLINICAL STUDIES).

CONTRAINDICATIONS

Hypersensitivity

Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients.

Monoamine Oxidase Inhibitors

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (*see* WARNINGS).

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.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. 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.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta, for a description of the risks of discontinuation of Cymbalta).

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 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 is not approved for use in treating bipolar depression.

Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of serious, sometimes fatal, reactions including 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. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

PRECAUTIONS

General

Hepatotoxicity — Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) 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.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. 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. Because it is possible that duloxetine and alcohol may interact to cause liver injury, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use.

Effect on Blood Pressure — In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

Activation of Mania/Hypomania — In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/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 — Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated with Cymbalta and 0% (0/777) of patients treated with placebo. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

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, Uncontrolled Narrow-Angle Glaucoma).

Discontinuation of Treatment with Cymbalta — Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

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 (*see* DOSAGE AND ADMINISTRATION).

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. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta 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. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

In clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 11 years, the mean baseline fasting blood glucose was 163 mg/dL, and the mean baseline hemoglobin $A1_c$ (HbA_{1c}) was 7.8%. In these studies, small increases in fasting blood glucose were observed in Cymbalta-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points. Overall diabetic control did not worsen as evidenced by stable HbA_{1c} values and by no differences in incidence of serious and non-serious diabetes-related adverse events relative to placebo or routine care.

Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Cymbalta.

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies Cymbalta has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that Cymbalta therapy does not affect their ability to engage in such activities.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions.

Although Cymbalta does not increase the impairment of mental and motor skills caused by 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.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding.

While patients with MDD may notice improvement with Cymbalta therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions (also *see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Potential for Other Drugs to Affect Cymbalta

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) 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).

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

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. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which 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.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs:

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* PRECAUTIONS, Hepatotoxicity).

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.

Potential for Interaction with 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.

Monoamine Oxidase Inhibitors — *See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, 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.

Pregnancy

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, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION).

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 and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or not duloxetine and/or its metabolites are excreted into human milk, but nursing while on Cymbalta is not recommended.

Pediatric Use

Safety and efficacy in pediatric patients have not been established (*see* WARNINGS, Clinical Worsening and Suicide Risk).

Geriatric Use

Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. 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.

ADVERSE REACTIONS

Cymbalta has been evaluated for safety in 2418 patients diagnosed with major depressive disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year.

Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping

similar types of events into a smaller number of standardized event categories is necessary. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

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

The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder

Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain

Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials

Major Depressive Disorder

Table 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating (*see* Table 1).

Table 1: Treatment-Emergent Adverse Events Incidence in MDD Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Cymbalta (N=1139)	Placebo (N=777)
Gastrointestinal Disorders		
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Metabolism and Nutrition Disorders		
Appetite decreased[2]	8	2
Investigations		
Weight decreased	2	1
General Disorders and Administration Site Conditions		
Fatigue	8	4
Nervous System Disorders		
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6	2
Vascular Disorders		
Hot flushes	2	1
Eye Disorders		
Vision blurred	4	1
Psychiatric Disorders		
Insomnia[3]	11	6
Anxiety	3	2
Libido decreased	3	1
Orgasm abnormal[4]	3	1
Reproductive System and Breast Disorders		
Erectile dysfunction[5]	4	1
Ejaculation delayed[5]	3	1
Ejaculatory dysfunction[5, 6]	3	1

[1] Events reported by at least 2% of patients treated with Cymbalta and more often with placebo. The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

[2] Term includes anorexia.

[3] Term includes middle insomnia.

[4] Term includes anorgasmia.

[5] Male patients only.

[6] Term includes ejaculation disorder and ejaculation failure.

Diabetic Peripheral Neuropathic Pain

Table 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the acute phase of DPN placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (*see* Table 2).

Table 2: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	Cymbalta 60 mg BID (N=225)	Cymbalta 60 mg QD (N=228)	Cymbalta 20 mg QD (N=115)	Placebo (N=223)
Gastrointestinal Disorders				
Nausea	30	22	14	9
Constipation	15	11	5	3
Diarrhea	7	11	13	6
Dry mouth	12	7	5	4
Vomiting	5	5	6	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1
General Disorders and Administration Site Conditions				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
Nervous System Disorders				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
Psychiatric Disorders				
Insomnia	13	8	9	7
Renal and Urinary Disorders				
Pollakiuria	5	1	3	2
Reproductive System and Breast Disorders				

Erectile dysfunction[2]	4	1	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

[1] Events reported by at least 2% of patients treated with Cymbalta and more often than placebo. The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.
[2] Male patients only.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 3 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials.

Table 3: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials[1]

	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
Adverse Event	**Cymbalta (N=378)**	**Placebo (N=247)**	**Cymbalta (N=761)**	**Placebo (N=530)**
Orgasm abnormal[2]	4	1	2	0
Ejaculatory dysfunction[3]	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

[1] Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.
[2] Term includes anorgasmia.
[3] Term includes ejaculation disorder and ejaculation failure.
NA=Not applicable.

Because adverse sexual events 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, as shown in Table 4 below, 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. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 4: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients		Female Patients	
	Cymbalta (n=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40**	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

n=Number of patients with non-missing change score for ASEX total.
*p=0.013 versus placebo.
**p<0.001 versus placebo.

Urinary Hesitation

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.

Laboratory Changes

Cymbalta treatment, for up to 9-weeks in MDD or 13-weeks in DPN 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* PRECAUTIONS).

Vital Sign Changes

Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS).

Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials and for up to 13-weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute.

Weight Changes

In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9-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.

Electrocardiogram Changes

Electrocardiograms were obtained from 321 Cymbalta-treated patients with major depressive disorder and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients.

Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Other Adverse Events Observed During the Premarketing Evaluation of Cymbalta for MDD and the Pain of DPN

Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with Cymbalta at multiple doses throughout the dose range studied during any phase of a trial within the premarketing database. The events included are those not already listed elsewhere in ADVERSE REACTIONS and not considered in the WARNINGS and PRECAUTIONS sections, that were reported with an incidence of greater than or equal to 0.05% and by more than one patient, are not common as background events and were considered possibly drug related (e.g., because of the drug's pharmacology) or potentially important.

It is important to emphasize that, although the events reported occurred during treatment with Cymbalta, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders — *Infrequent:* anemia, leukopenia, increased white blood cell count, lymphadenopathy, and thrombocytopenia.

Cardiac Disorders — *Infrequent:* atrial fibrillation, bundle branch block right, cardiac failure, cardiac failure congestive, coronary artery disease, and myocardial infarction.

Eye Disorders — *Infrequent:* diplopia, glaucoma, keroconjunctivitis sicca, macular degeneration, maculopathy, photopsia, and retinal detachment.

Gastrointestinal Disorders — *Frequent:* gastritis; *Infrequent:* apthous stomatitis, blood in stool, colitis, diverticulitis, dysphagia, esophageal stenosis acquired, gastric irritation, gastric ulcer, gingivitis, impaired gastric emptying, irritable bowel syndrome, lower abdominal pain, and melena.

General Disorders and Administration Site Conditions — *Frequent:* rigors; *Infrequent:* edema, feeling jittery, influenza-like illness, and thirst.

Hepato-biliary Disorders — *Infrequent:* hepatic steatosis.

Investigations — *Frequent:* weight increased; *Infrequent:* blood cholesterol increased, blood creatinine increased, and urine output decreased.

Metabolism and Nutrition Disorders — *Frequent:* hypoglycemia and increased appetite; *Infrequent:* dehydration, dyslipidemia, hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia.

Musculoskeletal and Connective Tissue Disorders — *Infrequent:* muscular weakness.

Nervous System Disorders — *Frequent:* hypoesthesia; *Infrequent:* ataxia and dysarthria.

Psychiatric Disorders — *Frequent:* initial insomnia, irritability, lethargy, nervousness, nightmare, restlessness, and sleep disorder; *Infrequent:* completed suicide, mania, mood swings, pressure of speech, sluggishness, and suicide attempt.

Renal and Urinary Disorders — *Frequent:* dysuria; *Infrequent:* micturition urgency, nephropathy, urinary hesitation, urinary incontinence, urinary retention, and urine flow decreased.

Respiratory, Thoracic and Mediastinal Disorders — *Infrequent:* oropharyngeal swelling.

Skin and Subcutaneous Tissue Disorders — *Frequent:* night sweats, pruritus, rash, and skin ulcer; *Infrequent:* acne, alopecia, cold sweat, exfoliative dermatitis, ecchymosis, eczema, erythema, face edema, hyperkeratosis, increased tendency to bruise, photosensitivity reaction, erythematous rash, and pruritic rash.

Vascular Disorders — *Infrequent:* hypertensive crisis, peripheral edema, and phlebitis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Duloxetine is not a controlled substance.

Physical and Psychological Dependence

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

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).

OVERDOSAGE

There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, as of October 2003, no cases of fatal acute overdose of Cymbalta have been reported. Four non-fatal acute ingestions of Cymbalta (300 to 1400 mg), alone or in combination with other drugs, have been reported.

Management of Overdose

There is no specific antidote to Cymbalta. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* PRECAUTIONS, Drug Interactions). The physician should consider

contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

Major Depressive Disorder

Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefits.

Diabetic Peripheral Neuropathic Pain

Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment (*see* CLINICAL PHARMACOLOGY, Special Populations *and* below).

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with Cymbalta. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Diabetic Peripheral Neuropathic Pain

As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was conducted.

Special Populations

Dosage for Renally Impaired Patients — Cymbalta is not recommended for patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 mL/min) (*see* CLINICAL PHARMACOLOGY).

Dosage for Hepatically Impaired Patients — It is recommended that Cymbalta not be administered to patients with any hepatic insufficiency (*see* CLINICAL PHARMACOLOGY *and* PRECAUTIONS).

Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* 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.

Discontinuing Cymbalta

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. 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.

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).

HOW SUPPLIED

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules are available in 20, 30, and 60 mg strengths.

The 20 mg* capsule has an opaque green body and cap, and is imprinted with "20 mg" on the body and "LILLY 3235" on the cap:

NDC 0002-3235-60 (PU3235) — Bottles of 60
NDC 0002-3235-33 (PU3235) — (ID†100) Blisters

The 30 mg* capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "LILLY 3240" on the cap:

NDC 0002-3240-30 (PU3240) — Bottles of 30
NDC 0002-3240-90 (PU3240) — Bottles of 90
NDC 0002-3240-04 (PU3240) — Bottles of 1000
NDC 0002-3240-33 (PU3240) — (ID†100) Blisters

The 60 mg* capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "LILLY 3237" on the cap:

NDC 0002-3237-30 (PU3237) — Bottles of 30
NDC 0002-3237-90 (PU3237) — Bottles of 90
NDC 0002-3237-04 (PU3237) — Bottles of 1000
NDC 0002-3237-33 (PU3237) — (ID†100) Blisters

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*equivalent to duloxetine base.
†Identi-Dose® (unit dose medication, Lilly).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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