

PV 3605 AMP

CYMBALTA®

(duloxetine hydrochloride) **Delayed-release Capsules**

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)
Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (CDD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

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 C₁₈H₁₉NOS+HCI, 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.

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, instaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monomie oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

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.

CYP2D6 and CYP1A2.

<u>Absorption and Distribution</u> — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lap}), 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 and evening dose as compared to a morning dose.

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 α₁-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 ¹⁴C-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 (<1½ 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

Special Populations
<u>Gender</u> — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

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 Cmax. 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.

Bace — 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, Cmax, 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 sultate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected increase further with multiple dosing. For this reason, Cymbalta is not recommended for patients with end-stage renal insease (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl] 3-00 mL/min) (see DOSAGE AND ADMINISTRATION). Population PK analyses suggest that mild to moderate degrees durabelities and calculated larges.

Henati dystunction (estimated circl 30-80 mit/min) have no significant effect on dutoxetine 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

Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions) Potential for Other Drugs to Affect Duloxetine Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

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 (in-14) the AUC was increased approximately 6-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

duloxetine (see PRECAUTIONS, Drug Interactions).

<u>Studies with Benzodiazepines</u>
<u>Lorazepam</u> — 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.

<u>Termazepam</u> — Under steady-state conditions for duloxetine (20 mg qhs) and termazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Potential for Duloxetine to Affect Other Drugs

<u>Drugs Metabolized by CYP1A2</u> — *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 pharmacokinetize 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 substrate.

substrates.

<u>Drugs Metabolized by CYP2D6</u> — 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).

<u>Drugs Metabolized by CYP2C9</u> — 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.

<u>Prugs Metabolized by CYP3A</u> — 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.

clinical studies have not been performed.

<u>Drugs Metabolized by CYP2C19</u> — 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. <u>Drugs Highly Bound to Plasma Protein</u>— 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=88 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=99) 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 impro 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.

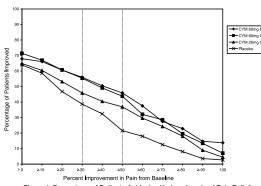
Diabetic Peripheral Neuropathic Pain

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 all teast 6 months. Study 1 and Fernolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had Type I or III diabetic peripheral neuropathy for at the controlled had Type I or III diabetic peripheral neuropathy for the controlled had Type I or III diabetic peripheral neuropathy for the controlled had Type I or III diabetic peripheral neuropathy for the controlled had Type I or III diabetic peripheral neuropathy for the controlled had Type I or III diabetic. The

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 24 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of a cetaminophen 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 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared Cymbalta 60 mg once to two to to the comparent of the comparent

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules



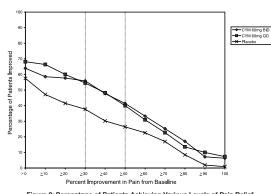


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

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).

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

De avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antipersesant medications, and this risk may persist until significant remission occurs. 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. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, CCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric incidications (obsessive compulsive disorder and social anxiety fiscing replaced in the MDD trials, but there were signals of risk arising rom some trials in other psychiatric incidications (obsessive compulsive disorder and social anxiety risk in pediatrial realizations). It is also unknown whether the suicidalities the suicidalities are considerable to the proper term use, i.e., bevond several months. It is also unknown whether the suicidalities. patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, 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, aggre 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.

established, there is concern that such symptoms may represent precursors to emerging sucioality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta, for a description of the risks of discontinuation of Cymbalta).

of discontinuation of Cymbalta).

Families and caregivers of pediatric 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 propt 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. Families and caregivers of adults being treated for depression should be similarly advised.

adults being treated for depression should be similarly advised.

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 represst 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 is not approved for use in treating bipolar depression.

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 intro lives never not usern evaluated in numans or animals. Ineretore, because Cymbalta in bitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be ombination with an MAOI, or within at least 14 days of discontinuing treatment with an Nad on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta be ting an MAOI.

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 (elevation was about two months. In controlled trials in MDN, elevations of ALT to 3-5 times the upper limit of normal occurred in 0.9% (8/830) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to 3-5 times the upper limit of normal occurred in 1.6% (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% (8/3732) of Cymbalta-treated patients. In the full cohort of placebo-controlled rails in any indication, 1% (8/3732) of Cymbalta-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, relecting 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

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

Effect on Blood Pressure— In MDO clinical trials, Cymbalta treatment was associated with man 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 placeb.

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

Activation of Manial/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% (1/1713) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mod disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with t

<u>Seizures</u> — 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).

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 Contractions.

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). Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules

<u>Use in Patients with Concomitant Illness</u> — 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, caulion is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or Cymbalar has not been systematically evaluated in patients wint a feed-in listory of myocardial infaction 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).

rate different from that in placebo-treated patients (see ADVERSE REACTIONS, Electrocardiognet Anages). In clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabeties was approximately 11 years, the mean baseline fragistic plucose was 163 mg/dl., and the mean baseline hemoglobin AT₀ (HbA₁₀) 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 HbA₁₀ 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 behalded.

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta hould not be administered to these patients (see CLINICAL PHARMACOLOGY and DOSAGE AND

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about
the benefits and risks associated with treatment with Cymbalta and should counsel them in its appropriate
use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for
Cymbalta. The prescriber or health professional should instruct patients, their families, and their caregivers to
read the Medication Guide and should assist them in understanding its contents. Patients should be given the
opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may
have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Cymbalta.

taking Cymbalta.

<u>Clinical Worsening and Suicide Risk</u> — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panio attacks, insommia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, owere not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. changes in the medication.

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be

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 and dizziness. 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 ordinanily 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.

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

uning 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 dvised to continue therapy as directed.

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

Drug Interactions (also see CLINICAL PHAHMACOLOGY, 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).

CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

Potential for Duloxetine to Affect Other Drugs

<u>Drugs Metabolized by CYP1A2</u> — 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).

<u>Drugs Metabolized by CYP2D6</u> — 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 nortriptylline, amiltriptyline, and impramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecianide), 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 arrhythmica dudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered.

Drugs Metabolized by CYP2AA — Results of in vitro studies demonstrate that duloxetine does not inhibit or

strouid not be co-administered.

<u>Drugs Metabolized by CYP3A</u> — 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:
<u>Alcohol</u> — 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). <u>CNS Acting Drugs</u> — Given the primary CNS effects of Cymbalta, it should be used with caution when it is ken 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 aphthol. 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 (in mEq) or Cymbalta with faminium- and magnesium-containing antacids (in mEq) or Cymbalta with faministration 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

<u>Carcinogenesis</u> — Duloxetine was administered in the diet to mice and rats for 2 years.

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/m² 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/m² 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/m² 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/m² 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/m² 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 aberation test in mouse bome 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) assays in primary rat hepatocytes, and did not induce esiter 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 80 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

Pregnancy

Pregnancy <u>Pregnancy Category C</u> — In animal reproduction studies, duloxetine has been shown to have adverse

enects on embryo/tetal and postnatal development.

When duloxetine was administered orally to regnant 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 of 120 mg/day on a mg/m² basis, in rats 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m² 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/m² basis in rabbits.)

When duloxetine was administered crally to necessar state the weights. When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of

writer duoxetime was administered drain to pregitant rats introughout gestaint and statation, me survival opps 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/m² basis), which are no-effect dose was 10 mg/kg/day. Fost-haviors 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. <u>Nonteratogenic Effects</u> — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake hibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization,

immioris (sivins), alse in the timin timester rave developed complications requiring priorionigen inspiral many 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, hypotrolina, hyperreflexia, tremor, jitteriness, irrability, feeding 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, Monamine 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

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). 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 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 frais, 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 180 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 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patients were exposed for at least 190 days and 445 Cymbalta-treated patient

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, 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.

resurs 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-ergent 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.

ion (assessment) of causality. The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and

in clear giose provide the pleasatier with scale basis to esamiliarily the feature commoditor or and an onor-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 investigations.



Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules

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).

Ornibation Peripheral Neuropathic Pain
Approximately 14% of the 588 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

Major Depressive Disorder 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 premarketing 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 Incide in MDD Placebo-Controlled Trials¹

	Percentage of Patients Reporting Event		
System Organ Class / Adverse 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		

- 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, nacopharyngitis, and upper respiratory tract infection.

 Term includes anorexia.

 Term includes anorexia.

 Term includes anorexia.

 Term includes anorexia.

 Term includes anorexia.

- Male patients only
- 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 premarketing 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 asthanic (see Table 2). patients) were: nausea; so and asthenia (see Table 2).

Table 2: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials¹

	Percentage of Patients Reporting Event			
System Organ Class / Adverse 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		6		2
Hyperhidrosis	8	6	6	2

- 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, arthrafaja, pain in extremity, and
- 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 orduct labeling are likely to underestimate their extual incidence. Table 3 disclays the incidence of sexual 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

	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	

- Events reported by at least 2% of patients treated with Cymbalta and more often than with pla Term includes anormasmia
- Term includes ejaculation disorder and ejaculation failure.

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 difficully with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than 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		

ssing change score for ASEX total *p=0.013 versus placebo. **p<0.001 versus placebo.



Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules

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 drugseleted. 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 Cymbalta treatment, for up to 9-weeks in initial placebo-controlled unifical intais of 40 to 120 mg damy 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).

THE UTILITY OF THE CAPITIONS.

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

Weight Changes In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9-weeks experienced a san weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in scebo-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 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 OT (OTc) interval in
Cymbalta-treated patients id id 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

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 OT (OTc) interval in Cymbalta-treated patients di

observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial 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 and postmarketing database. The events included are those not already listed in both Table 1 and Table 2 and not considered in the WARNINGS and PRECAUTIONS sections. The events 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.

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 Cymbalian, 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; infrequent adverse 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 — Frequent: palpitations; Infrequent: atrial fibrillation, bundle branch block right, cardiac failure, cardiac failure congestive, coronary artery disease, myocardial infarction, and tachycardia.

Ear and Labyrinth Disorders — Frequent: verigo.

Eye Disorders — Frequent: vision blurred; Infrequent: diplopia, glaucoma, keroconjunctivitis sicca, macular degeneration, maculopathy, photopsia, retinal detachment, and visual disturbance.

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

and stomatitis.

General Disorders and Administration Site Conditions — Frequent: asthenia; Infrequent: edema, feeling abnormal, feeling hot and/or cold, feeling jittery, influenza-like illness, malaise, rigors, and thirst.

Hepato-biliary Disorders — Infrequent: hepatic steatosis.

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

Metabolism and Nutrition Disorders — Frequent: hypoglycemia and increased appetite; nfrequent: dehydration, dyslipidemia, hypercholesterolemia, hypertipidemia, and hypertriglyceridemia.

Musculoskeletal and Connective Tissue Disorders — Frequent: muscle tightness and muscle twitching; nfrequent: muscular weakness.

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

Nervous System Disorders — Frequent: dysgeusia and hypoesthesia; Infrequent: ataxia and dysarthna. Psychiatric Disorders — Frequent: anorgasmia, anxiety, hypersonnia, initial insomnia, intrainismomia, ribidio decreased, middle insomnia, nervousness, nightmare, restlessness, and sleep disorder; Infrequent: agitation, bruxism, completed suicide, disorientation, loss of libido, mania, mood swings, orgasm abnormal, pressure of speech, sluggishness, suicide attempt, and tension.

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

Reproductive System and Breast Disorders — Frequent: ejaculation delayed and ejaculation disorder.

Respiratory, Thoracic and Mediastinal Disorders — Frequent: yawning; Infrequent: oropharyngeal swelling.

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

Vascular Disorders — Frequent: hot flush; Infrequent: flushing, hypertensive crisis, peripheral coldness, peripheral edema, and phlebitis

Postmarketing Spontaneous Reports

Adverse events reported since market introduction that were temporally related to Cymbalta therapy include rash reported rarely and the following adverse events reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, glaucoma, hepatitis, hyponatremia, jaundice, orthostatic hypotension (especially at the initiation of treatment), Stevens-Johnson Syndrome, syncope (especially at initiation of treatment), and urticaria.

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 or 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

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 insections of Cymbalta (200 to 1400 mn), alone or in combination with other drugs, have been reported. Management of Overdose

management or uverdose

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.

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-thing 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 volves patients who are taking or have recently taken Cymbalta and might ingest excessive quantities of a

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 recease 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

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

I nere 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/Confirmation/Extended Technology.

Maintenance/Continuation/Extended Treatment

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

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).

 ${\color{red} \textbf{HOW SUPPLIED}} \\ \textbf{Cymbalta} \\ \text{@ (duloxetine hydrochloride) Delayed-release Capsules are available in 20, 30, and 60 mg} \\$

Ornitorial Unifortenine Hydrochinology Delaysochelease capsulas are available in 20, 30, and 30 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 0002-3235-60 (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 0002-3240-90 (PU3240) — Bottles of 90
NDC 0002-3240-04 (PU3240) — Bottles of 1000
NDC 0002-3240-04 (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 "LLLY 3237" on the cap:
NDC 0002-3237-30 (PU3237) — Bottles of 30
NDC 0002-3237-90 (PU3237) — Bottles of 90
NDC 0002-3237-90 (PU3237) — Bottles of 1000
NDC 0002-3237-33 (PU3237) — (ID†100) Blisters

†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] Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules

Medication Guide

About Using Antidepressants in Children and Teenagers What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

- 1. There is a risk of suicidal thoughts or actions
- 2. How to try to prevent suicidal thoughts or actions in your child 3. You should watch for certain signs if your child is taking an antidepressant
- 4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts

and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called suicidality or being suicidal. A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. No one committed suicide in these studies, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include

- Bipolar illness (sometimes called manic-depressive illness)
- . A family history of bipolar illness
- · A personal or family history of attempting suicide

any of these are present, make sure you tell your health care provider before your child takes an

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child

After starting an antidepressant, your child should generally see his or her health care provider

· Once a week for the first 4 weeks

. Every 2 weeks for the next 4 weeks

· After taking the antidepressant for 12 weeks After 12 weeks, follow your health care provider's advice about how often to come back

 More often if problems or questions arise (see Section 3) You should call your child's health care provider between visits if needed

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

- Contact your child's health care provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:
- · Thoughts about suicide or dying
- · Attempts to commit suicide
- · Feeling very agitated or restless
- · Panic attacks
- · Difficulty sleeping (insomnia)
- · New or worse irritability Acting aggressive, being angry, or violent
- · Acting on dangerous impulses · An extreme increase in activity and talking

 Other unusual changes in behavior or mood Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression. For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or

Is this all I need to know if my child is being prescribed an antidepressant? No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company

Zoloft[®] is a registered trademark of Pfizer Pharmaceuti Anafranil[®] is a registered trademark of Mallinckrodt Inc This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Literature revised September 22, 2005

Eli Lilly and Company Indianapolis, IN 46285, USA

www.Cymbalta.com

PV 3605 AMP PRINTED IN USA Copyright © 2004, 2005, Eli Lilly and Company. All rights reserved.