



# CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules

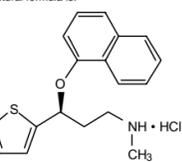
## WARNING

**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 (OCD), 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 (+)-(-)-N-methyl-γ-(1-naphthylthio)-2-thiophenepropylamine hydrochloride. The empirical formula is C<sub>18</sub>H<sub>19</sub>NOS<sub>2</sub>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 one or two delayed-release pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. The extended-release 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 10 to 16 hours and it marginally decreases the  $AUC_{0-24}$  by about 10%. There is a 3-hour delay in absorption and a one-third decrease 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  $\alpha_1$ -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 <sup>14</sup>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 metabolic pathways for duloxetine are 4-hydroxy, 5-hydroxy, 6-methoxy duloxetine formed 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. 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. 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 and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 10-fold higher and were 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 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

**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 isozyme *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, the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroid 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.

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**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 (HAM-D-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 731 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  $\geq 4$  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.

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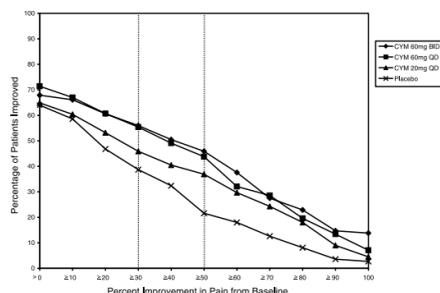


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

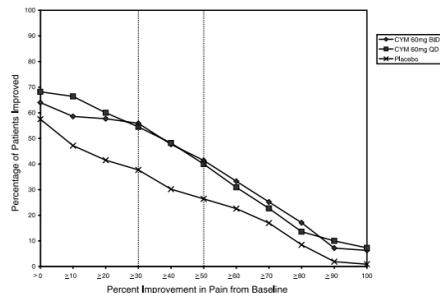


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

## 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 (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant improvement has been achieved. 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.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, 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 indications (beyond severe compulsive disorder and social anxiety disorder) as well as in patients with other psychiatric disorders. It is unknown whether the suicidality risk in pediatric 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 telephone may be appropriate in between face-to-face visits.**

**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, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta, for a description of the risks 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 report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of 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 represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta 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 serotonin syndrome-like 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 used MAOIs. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of duloxetine 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% (31/9454) of Cymbalta-treated patients.

Blood pressure should be measured prior to initiation of 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 with 8- 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., paresthesia 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.

Cymbalta 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).

(duloxetine hydrochloride)  
Delayed-release Capsules

CYMBALTA®  
PV 3605 AMP

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

**Use in Patients with Concomitant Illness** — Clinical experience with Cymbalta in patients with



## 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).

## 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 3.0%, 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 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 Incidence in MDD Placebo-Controlled Trials<sup>1</sup>

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

<sup>1</sup> 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.

<sup>2</sup> Term includes anorexia.

<sup>3</sup> Term includes middle insomnia.

<sup>4</sup> Term includes anorgasmia.

<sup>5</sup> Male patients only.

<sup>6</sup> 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 asthenia (see Table 2).

Table 2: Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials<sup>1</sup>

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)
<b>Gastrointestinal Disorders</b>				
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
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
<b>Infections and Infestations</b>				
Nasopharyngitis	9	7	9	5
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
<b>Nervous System Disorders</b>				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
<b>Psychiatric Disorders</b>				
Insomnia	13	8	9	7
<b>Renal and Urinary Disorders</b>				
Pollakiuria	5	1	3	2
<b>Reproductive System and Breast Disorders</b>				
Erectile dysfunction <sup>2</sup>	4	1	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Hyperhidrosis	8	6	6	2

<sup>1</sup> 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.

<sup>2</sup> 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<sup>1</sup>

Adverse Event	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
	Cymbalta (N=376)	Placebo (N=247)	Cymbalta (N=761)	Placebo (N=530)
Orgasm abnormal <sup>2</sup>	4	1	2	0
Ejaculatory dysfunction <sup>3</sup>	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

<sup>1</sup> Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.

<sup>2</sup> Term includes anorgasmia.

<sup>3</sup> 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 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

Adverse Event	Male Patients		Female Patients	
	Cymbalta (n=175)	Placebo (n=63)	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.

## 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 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 160 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, QRS, or QTc 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 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.

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; 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** — *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:* vertigo.

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

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

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

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

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

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

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

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

**Psychiatric Disorders** — *Frequent:* anorgasmia, anxiety, hypersomnia, initial insomnia, irritability, lethargy, libido 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, suicidal ideation, 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; *Infrequent:* acne, alopecia, cold sweat, ecchymosis, eczema, erythema, erythematous rash, exfoliative dermatitis, face edema, hyperkeratosis, increased tendency to bruise, photosensitivity reaction, and pruritic rash.

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

## 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 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<sub>max</sub> 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 estimated 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