glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, CYMBALTA was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the CYMBALTA group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the CYMBALTA group and by 0.2% in the routine care group.

5.15 Urinary Hesitation and Retention

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

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Orthostatic Hypotension, Falls and Syncope *[see Warnings and Precautions (5.3)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.4)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[see Warnings and Precautions (5.7)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.8)]*
- Angle-Closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Increases in Blood Pressure *[see Warnings and Precautions (5.11)]*
- Clinically Important Drug Interactions *[see Warnings and Precautions (5.12)]*
- Hyponatremia *[see Warnings and Precautions (5.13)]*
- Urinary Hesitation and Retention *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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

The stated frequencies of adverse reactions represent the proportion of patients who experienced, at least once, one treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Reactions in Adults

Adult Clinical Trial Database

The data described below reflect exposure to CYMBALTA in placebo-controlled adult trials for MDD (N=3779), GAD (N=1018), OA (N=503), CLBP (N=600), DPNP (N=906), and FM (N=1294). The age range in this pooled population was 17 to 89 years of age. In this pooled population, 66%, 61%, 61%, 43%, and 94% of adult patients were female; and 82%, 73%, 85%, 74%, and 86% of adult patients were Caucasian in the MDD, GAD, OA and CLBP, DPNP, and FM populations, respectively. Most patients received CYMBALTA dosages of a total of 60 to 120 mg per day *[see Clinical Studies (14)]*. The data below do not include results of the trial that evaluated the efficacy of CYMBALTA for the treatment of GAD in patients ≥65 years old (Study GAD-5) *[see Clinical Studies (14.3)]*; however, the adverse reactions observed in this geriatric population were generally similar to adverse reactions in the overall adult population.

Adverse Reactions Leading to Treatment Discontinuation in Adult Placebo-Controlled Trials

Major Depressive Disorder

Approximately 8.4% (319/3779) of CYMBALTA-treated patients in placebo-controlled adult trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2536) of placebo-treated patients. Nausea (CYMBALTA 1.1%, placebo 0.4%) was the only adverse reaction reported as a 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-treated patients).

Generalized Anxiety Disorder

Approximately 13.7% (139/1018) of the CYMBALTA-treated patients in placebo-controlled adult trials for GAD discontinued treatment due to an adverse reaction, compared with 5% (38/767) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA 3.3%, placebo 0.4%), and dizziness (CYMBALTA 1.3%, placebo 0.4%).

Diabetic Peripheral Neuropathic Pain

Approximately 12.9% (117/906) of the CYMBALTA-treated patients in placebo-controlled adult trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA 3.5%, placebo 0.7%), dizziness (CYMBALTA 1.2%, placebo 0.4%), and somnolence (CYMBALTA 1.1%, placebo 0%).

Fibromyalgia

Approximately 17.5% (227/1294) of the CYMBALTA-treated patients in 3- to 6-month placebo-controlled adult trials for FM discontinued treatment due to an adverse reaction, compared with 10.1% (96/955) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA 2.0%, placebo 0.5%), headache (CYMBALTA 1.2%, placebo 0.3%), somnolence (CYMBALTA 1.1%, placebo 0%), and fatigue (CYMBALTA 1.1%, placebo 0.1%).

Chronic Pain due to Osteoarthritis

Approximately 15.7% (79/503) of the CYMBALTA-treated patients in 13-week, placebo-controlled adult trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 7.3% (37/508) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA 2.2%, placebo 1%).

Chronic Low Back Pain

Approximately 16.5% (99/600) of the CYMBALTA-treated patients in 13-week, placebo-controlled adult trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (CYMBALTA 3%, placebo 0.7%), and somnolence (CYMBALTA 1%, placebo 0%).

Most Common Adverse Reactions in Adult Trials

The most commonly observed adverse reactions in CYMBALTA-treated patients (as defined above) were:

- Diabetic Peripheral Neuropathic Pain: nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.
- Fibromyalgia: nausea, dry mouth, constipation, somnolence, decreased appetite, hyperhidrosis, and agitation.
- Chronic Pain due to Osteoarthritis: nausea, fatigue, constipation, dry mouth, insomnia, somnolence, and dizziness.
- Chronic Low Back Pain: nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

The most commonly observed adverse reactions in CYMBALTA-treated patients in all the pooled adult populations (i.e., MDD, GAD, DPNP, FM, OA, and CLBP) (incidence of at least 5% and at least twice the incidence in placebo-treated patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

Table 2 displays the incidence of adverse reactions in placebo-controlled trials for approved adult populations (i.e., MDD, GAD, DPNP, FM, OA, and CLBP) that occurred in 5% or more of CYMBALTA-treated patients and with an incidence greater than placebo-treated patients.

Table 2: Adverse Reactions: Incidence of 5% or More and Greater than Placebo in Placebo-Controlled Trials of Approved Adult Populations[a]

Adverse Reaction	Percentage of Patients Reporting Reaction	
	CYMBALTA (N=8100)	Placebo (N=5655)
Nausea[c]	23	8
Headache	14	12
Dry mouth	13	5
Somnolence[e]	10	3
Fatigue[b,c]	9	5
Insomnia[d]	9	5
Constipation[c]	9	4
Dizziness[c]	9	5
Diarrhea	9	6
Decreased appetite[c]	7	2
Hyperhidrosis[c]	6	1
Abdominal pain[f]	5	4

[a] Includes adults with MDD, GAD, DPNP, FM, and chronic musculoskeletal pain. The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.
[b] Also includes asthenia.
[c] Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
[d] Also includes initial insomnia, middle insomnia, and early morning awakening.
[e] Also includes hypersomnia and sedation.
[f] Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

Adverse Reactions in Pooled MDD and GAD Trials in Adults

Table 3 displays the incidence of adverse reactions in MDD and GAD placebo-controlled adult trials that occurred in 2% or more of CYMBALTA-treated patients and with an incidence greater than placebo-treated patients.

Table 3: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in MDD and GAD Placebo-Controlled Trials in Adults[a,b]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	CYMBALTA (N=4797)	Placebo (N=3303)
Cardiac Disorders		
Palpitations	2	1
Eye Disorders		
Vision blurred	3	1
Gastrointestinal Disorders		
Nausea[c]	23	8
Dry mouth	14	6
Constipation[c]	9	4
Diarrhea	9	6
Abdominal pain[d]	5	4
Vomiting	4	2
General Disorders and Administration Site Conditions		
Fatigue[e]	9	5
Metabolism and Nutrition Disorders		
Decreased appetite[c]	6	2
Nervous System Disorders		
Headache	14	14
Dizziness[c]	9	5
Somnolence[f]	9	3
Tremor	3	1

8.10 Severe Renal Impairment

Limited data are available on the effects of CYMBALTA in patients with end-stage renal disease (ESRD). After a single 60 mg dose of CYMBALTA, C_{max} and AUC values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. Population PK analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance *[see Dosage and Administration (2.7) and Warnings and Precautions (5.14)]*.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

While CYMBALTA has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of CYMBALTA (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

9.3 Dependence

In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

10 OVERDOSAGE

10.1 Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute CYMBALTA overdoses, primarily with mixed overdoses, but also with CYMBALTA only, including 1000 mg of CYMBALTA (approximately 8.3 times the maximum recommended dosage). Signs and symptoms of overdose (CYMBALTA alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

10.2 Management of Overdose

There is no specific antidote to a CYMBALTA overdosage, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.

In case of acute overdose with CYMBALTA, treatment should consist of those general measures employed in the management of overdose with any drug, such as assuring an adequate airway, oxygenation, and ventilation and monitoring cardiac rhythm and vital signs. 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. Induction of emesis is not recommended.

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

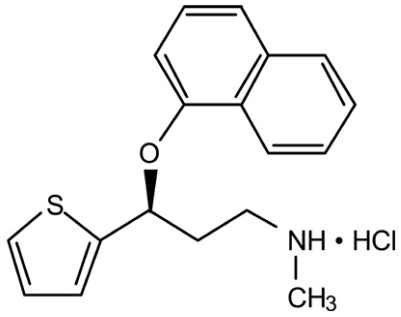
In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who overdose with CYMBALTA and tricyclic antidepressants. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Consider contacting a poison control center (1-800-222-1222 or www.poison.org) for additional information on the treatment of overdosage.

11 DESCRIPTION

CYMBALTA® (duloxetine delayed-release capsules) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine

hydrochloride. The empirical formula is $C_{18}H_{19}NOS•HCl$, which corresponds to a molecular weight of 333.88. The structural formula is:



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

Each capsule contains enteric-coated pellets of 20, 30, or 60 mg of duloxetine (equivalent to 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride, 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

12.2 Pharmacodynamics

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).

CYMBALTA is in a class of drugs known to affect urethral resistance *[see Warnings and Precautions (5.15)]*.

Cardiac Electrophysiology

The effect of CYMBALTA 160 mg and 200 mg administered twice daily (2.7 and 3.3 times the maximum recommended dosage, respectively) to steady state was evaluated in a randomized, double-blinded, two-way crossover study in 117 healthy female adult subjects. No QT interval prolongation was detected. CYMBALTA appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

12.3 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, CYP1A2 and CYP2D6.

Absorption

After oral CYMBALTA administration, 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. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

Effect of Food: 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%.

Distribution

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-acid glycoprotein. The interaction between duloxetine and other highly protein

bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Elimination

Metabolism

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 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.

Excretion

Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Specific Populations

Pediatric Patients

Duloxetine steady-state plasma concentration was comparable in pediatric patients 7 to 17 years of age and adult patients. The average steady-state duloxetine concentration was approximately 30% lower in this pediatric population relative to adult patients. The model-predicted duloxetine steady state plasma concentrations in pediatric patients 7 to 17 years of age were mostly within the concentration range observed in adult patients and did not exceed the concentration range in adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (3 times the maximum recommended human dose (MRHD) of 120 mg/day given to children on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (1 time the MRHD given to children). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (2 times the MRHD given to children).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (1 time the MRHD given to children) and up to 36 mg/kg/day in males (1.4 times the MRHD given to children) did not increase the incidence of tumors.

Mutagenesis

Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility

Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (3 times the MRHD given to adolescents on a mg/m^2 basis) did not alter mating or fertility.

14 CLINICAL STUDIES

14.1 Overview of the Clinical Trials

The efficacy of CYMBALTA has been established in the following populations in adequate and well-controlled trials:

- Major Depressive Disorder (MDD): 4 short-term (Studies MDD-1, MDD-2, MDD-3, and MDD-4) and 1 maintenance trial (Study MDD-5) in adults *[see Clinical Studies (14.2)]*.

- Generalized Anxiety Disorder (GAD): 3 short-term trials in adults (Studies GAD-1, GAD-2, and GAD-3), 1 maintenance trial in adults (Study GAD-4), 1 short-term trial in geriatric patients (Study GAD-5), and 1 short-term trial in pediatric patients 7 to 17 years of age (Study GAD-6) *[see Clinical Studies (14.3)]*.
- Diabetic Peripheral Neuropathic Pain (DPNP): Two 12-week trials in adults (Studies DPNP-1 and DPNP-2) *[see Clinical Studies (14.4)]*.
- Fibromyalgia (FM): Two trials in adults (one of 3 months duration and one of 6 months duration) (Studies FM-1 and FM-2) and one 13-week trial in pediatric patients 13 to 17 years of age (Study FM-4) *[see Clinical Studies (14.5)]*.
- Chronic Musculoskeletal Pain: Two 12- to 13-week trials in adult patients with chronic low back pain (CLBP) (Studies CLBP-1 and CLBP-3) and one 13-week trial in adult patients with chronic pain due to osteoarthritis (OA) (Study OA-1) *[see Clinical Studies (14.6)]*.

Additionally, a summary of the following trials that did not demonstrate efficacy are presented below: Study FM-3 (a 16-week trial in adult patients with fibromyalgia), Study CLBP-2 (a 13-week trial in adult patients with CLBP), and Study OA-2 (a 13-week trial in adult patients with chronic pain due to OA).

14.2 Major Depressive Disorder in Adults

The efficacy of CYMBALTA as a treatment for MDD in adults was established in 4 randomized, double-blind, placebo-controlled, fixed-dose trials in adult outpatients (18 to 83 years) meeting DSM-IV criteria for MDD:

- In Studies MDD-1 and MDD-2, 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 Study MDD-3, 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 Study MDD-4, patients were randomized to CYMBALTA 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks.

In all four trials, CYMBALTA demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score (see Table 8). There is no evidence that doses greater than 60 mg/day confer additional benefits.

In all of these clinical trials, 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.

Table 8: Summary of the Primary Efficacy Results for Adult Trials in MDD

Study Number	Treatment Group	Primary Efficacy Measure: HAMD-17		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study MDD-1	CYMBALTA (60 mg/day)[b]	21.5 (4.10)	-10.9 (0.70)	-4.9 (-6.8, -2.9)
	Placebo	21.1 (3.71)	-6.1 (0.69)	--
Study MDD-2	CYMBALTA (60 mg/day)[b]	20.3 (3.32)	-10.5 (0.71)	-2.2 (-4.0, -0.3)
	Placebo	20.5 (3.42)	-8.3 (0.67)	--
Study MDD-3	CYMBALTA (20 mg BID)[b]	18.6 (5.85)	-7.4 (0.80)	-2.4 (-4.7, -0.2)
	CYMBALTA (40 mg BID)[b]	18.1 (4.52)	-8.6 (0.81)	-3.6 (-5.9, -1.4)
	Placebo	17.2 (5.11)	-5.0 (0.81)	--
Study MDD-4	CYMBALTA (40 mg BID)[b]	19.9 (3.54)	-11.0 (0.49)	-2.2 (-3.6, -0.9)
	CYMBALTA (60 mg BID)[b]	20.2 (3.41)	-12.1 (0.49)	-3.3 (-4.7, -1.9)
	Placebo	19.9 (3.58)	-8.8 (0.50)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were included.

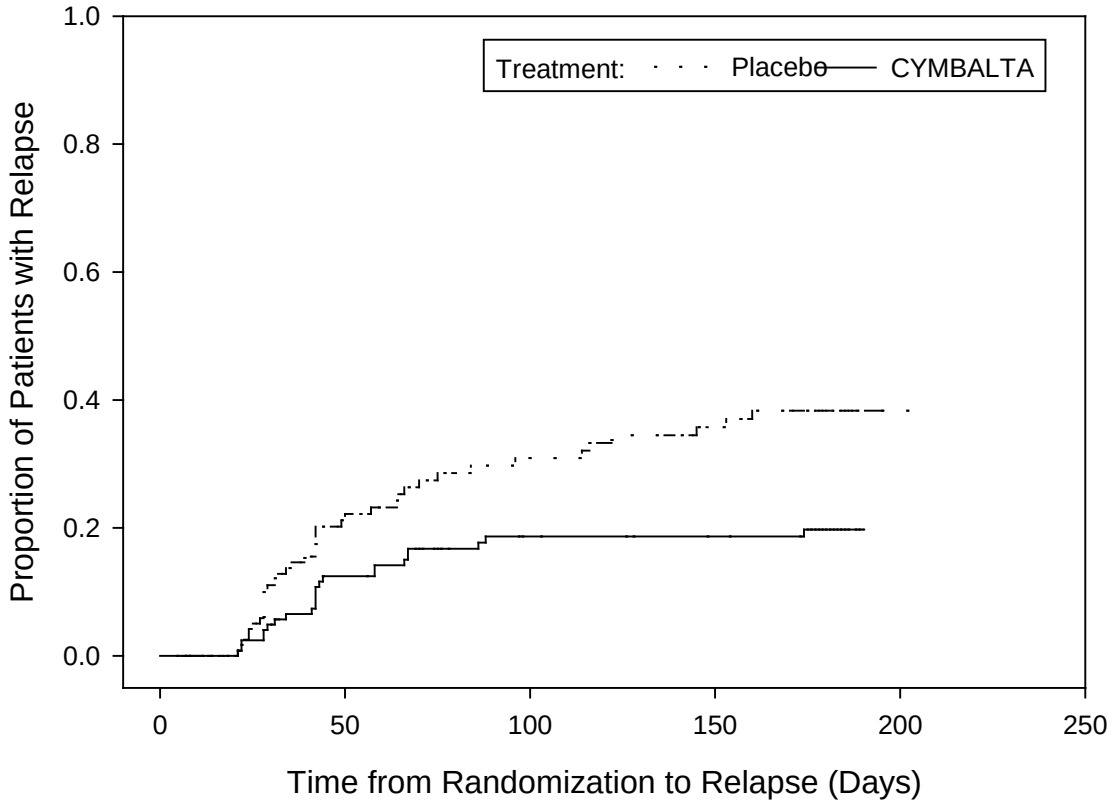
[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Doses statistically significantly superior to placebo.

In Study MDD-5, 533 adult patients meeting DSM-IV criteria for MDD received CYMBALTA 60 mg once daily during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who responded to open label treatment [defined as meeting the following criteria at weeks 10 and 12: a HAMD-17 total score ≤9, Clinical Global Impressions of Severity (CGI-S) ≤2, and not meeting the DSM-IV criteria for MDD] were randomly assigned to continuation of CYMBALTA at the same dosage (N=136) or to placebo (N=142) for 6 months.

In Study MDD-5, patients on CYMBALTA experienced a statistically significantly longer time to relapse of depression than did patients on placebo (see Figure 1). Relapse was defined as an increase in the CGI-S score of ≥2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit.

Figure 1: Cumulative Proportion[a] of Adult Patients with MDD Relapse (Study MDD-5)



[a] Kaplan-Meier estimator method.

14.3 Generalized Anxiety Disorder

GAD Trials in Adults (Including Geriatric Patients)

The efficacy of CYMBALTA in the treatment of generalized anxiety disorder (GAD) was established in 1 fixed-dose randomized, double-blind, placebo-controlled trial and 2 flexible-dose randomized, double-blind, placebo-controlled trials in adult outpatients between 18 and 83 years of age meeting the DSM-IV criteria for GAD (Studies GAD-1, GAD-2, and GAD-3, respectively).

In Studies GAD-1 and GAD-2, the starting dose was 60 mg once daily (down titration to 30 mg once daily was allowed for tolerability reasons; the dosage could be increased to 60 mg once daily). Fifteen percent of patients were down titrated. Study GAD-3 had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

Studies GAD-2 and GAD-3 involved dose titration with CYMBALTA doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dosage for completers at endpoint in these trials was 104.8 mg/day. Study GAD-1 evaluated CYMBALTA dosages of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

In all 3 trials, CYMBALTA demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score (see Table 8) and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a composite measurement of the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities, and family life/home responsibilities.

In Study GAD-4, 887 patients meeting DSM-IV-TR criteria for GAD received CYMBALTA 60 mg to 120 mg once daily during an initial 26-week open-label treatment phase. Four hundred and twenty-nine patients who responded to open-

label treatment [defined as meeting the following criteria at weeks 24 and 26: a decrease from baseline HAM-A total score by at least 50% to a score no higher than 11, and a Clinical Global Impressions of Improvement (CGI-Improvement) score of 1 or 2] were randomly assigned to continuation of CYMBALTA at the same dosage (N=216) or to placebo (N=213) and were observed for relapse. Of the patients randomized, 73% had been in a responder status for at least 10 weeks. Relapse was defined as an increase in CGI-Severity score at least 2 points to a score ≥4 and a MINI (Mini-International Neuropsychiatric Interview) diagnosis of GAD (excluding duration), or discontinuation due to lack of efficacy. Patients taking CYMBALTA experienced a statistically significantly longer time to relapse of GAD than did patients taking placebo (see Figure 2).

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

GAD Trial in Geriatric Patients

The efficacy of CYMBALTA in the treatment of patients ≥65 years of age with GAD was established in one 10-week flexible-dose, randomized, double-blind, placebo-controlled trial in adults ≥65 years of age meeting the DSM-IV criteria for GAD (Study GAD-5). In Study GAD-5, the starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments at treatment weeks 2, 4, and 7 up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week acute treatment phase was 51 mg. Patients treated with CYMBALTA (N=151) demonstrated significantly greater improvement compared with placebo (N=140) on mean change from baseline to endpoint as measured by the HAM-A total score (see Table 8).

GAD Trial in Pediatric Patients 7 to 17 Years Old

The efficacy of CYMBALTA in the treatment of pediatric patients 7 to 17 years of age with GAD was established in 1 flexible-dose randomized, double-blind, placebo-controlled trial in pediatric outpatients with GAD (based on DSM-IV criteria) (Study GAD-6).

In Study GAD-6, the starting dosage was 30 mg once daily for 2 weeks. Further dosage increases in 30 mg increments up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week treatment phase was 57.6 mg/day. In this study, CYMBALTA (N=135) demonstrated superiority over placebo (N=137) from baseline to endpoint as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score (see Table 9).

Table 9: Summary of the Primary Efficacy Results for GAD Trials

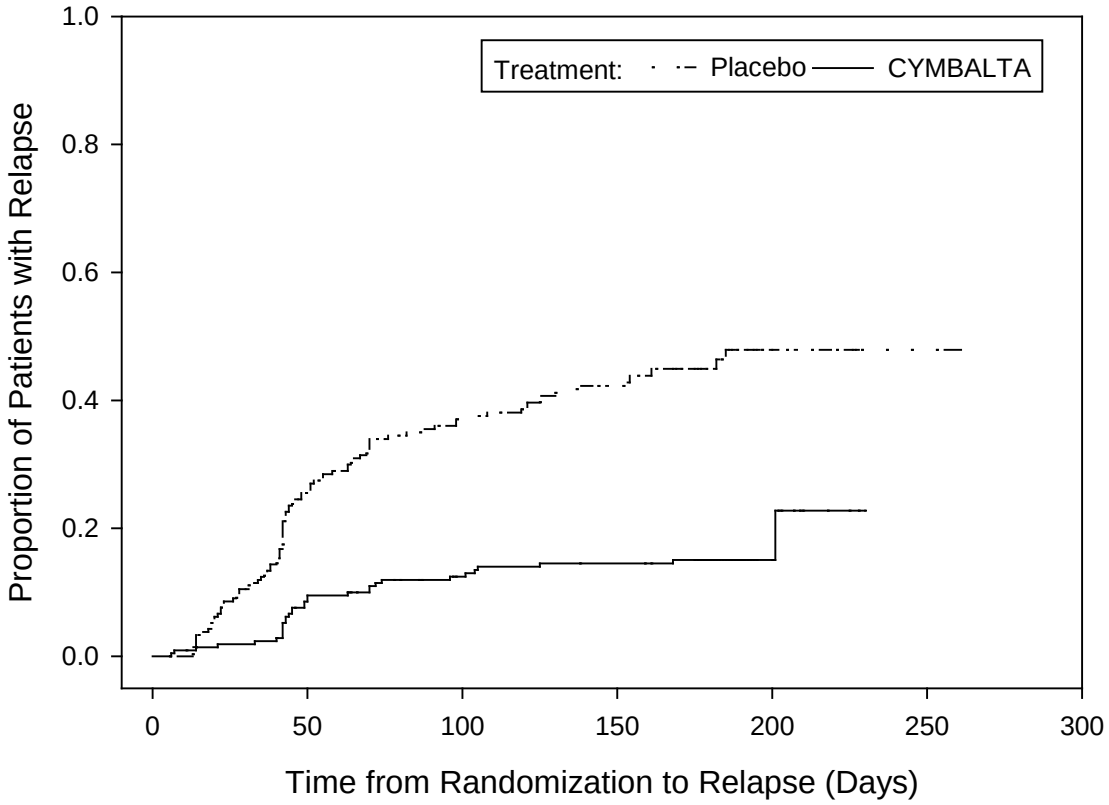
Study Number (population) (measurement)	Treatment Group	Primary Efficacy Measure		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study GAD-1 (Adult) (HAM-A)	CYMBALTA (60 mg/day)[b]	25.1 (7.18)	-12.8 (0.68)	-4.4 (-6.2, -2.5)
	CYMBALTA (120 mg/day)[b]	25.1 (7.24)	-12.5 (0.67)	-4.1 (-5.9, -2.3)
	Placebo	25.8 (7.66)	-8.4 (0.67)	--
Study GAD-2 (Adult) (HAM-A)	CYMBALTA (60-120 mg/day)[b]	22.5 (7.44)	-8.1 (0.70)	-2.2 (-4.2, -0.3)
	Placebo	23.5 (7.91)	-5.9 (0.70)	--
Study GAD-3 (Adult) (HAM-A)	CYMBALTA (60-120 mg/day)[b]	25.8 (5.66)	-11.8 (0.69)	-2.6 (-4.5, -0.7)
	Placebo	25.0 (5.82)	-9.2 (0.67)	--
Study GAD-5 (Geriatric) (HAM-A)	CYMBALTA (60-120 mg/day)[b]	24.6 (6.21)	-15.9 (0.63)	-4.2 (-5.9, -2.5)
	Placebo	24.5 (7.05)	-11.7 (0.67)	--
Study GAD-6 (Pediatric) (PARS for GAD)	CYMBALTA (30-120 mg/day)[b]	17.5 (1.98)	-9.7 (0.50)	-2.7 (-4.0, -1.3)
	Placebo	17.4 (2.24)	-7.1 (0.50)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were included.

[a] Difference (drug minus placebo) in least squares mean change from baseline.

[b] Dose statistically significantly superior to placebo.

Figure 2: Cumulative Proportion[a] of Adult Patients with GAD Relapse (Study GAD-4)



[a] Kaplan-Meier estimator method.

14.4 Diabetic Peripheral Neuropathic Pain in Adults

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

Both trials compared CYMBALTA 60 mg once daily or 60 mg twice daily with placebo. Study DPNP-1 additionally compared CYMBALTA 20 mg with placebo. A total of 457 patients (342 CYMBALTA, 115 placebo) were enrolled in Study DPNP-1 and a total of 334 patients (226 CYMBALTA, 108 placebo) were enrolled in Study DPNP-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 scores from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figures 3 and 4 show the fraction of patients achieving that degree of improvement in Studies DPNP-1 and DPNP-2, respectively. 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 trial were assigned 0% improvement. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the trial.

Figure 3: Percentage of DPNP Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study DPNP-1)

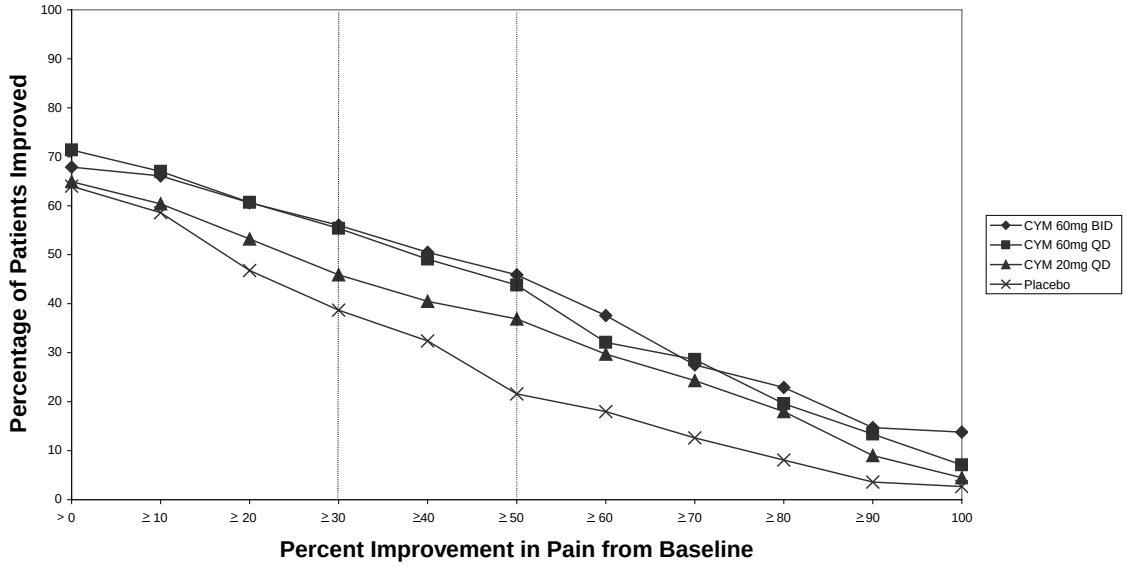
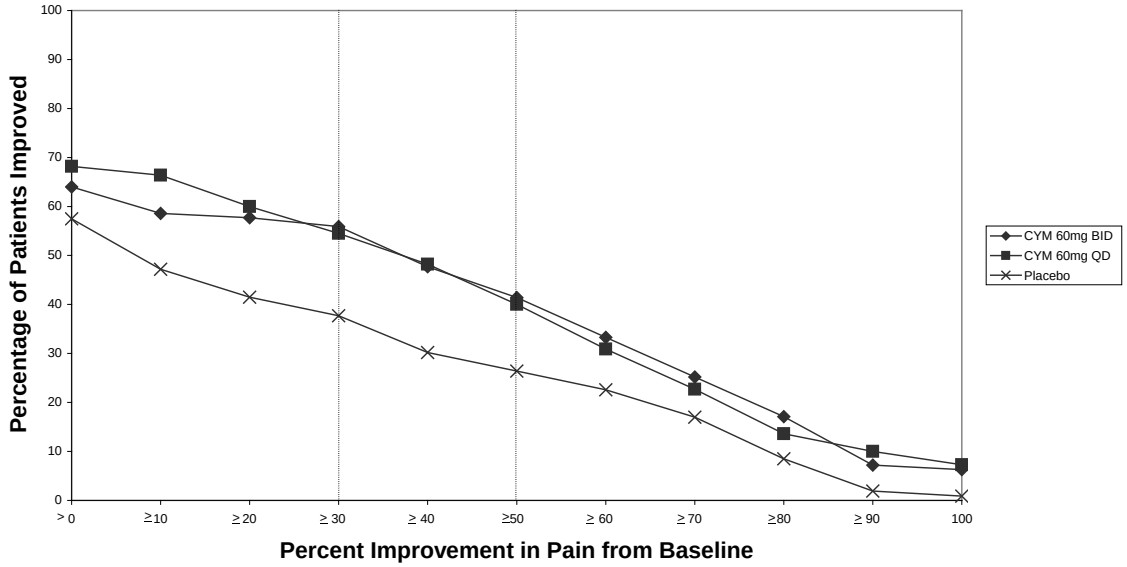


Figure 4: Percentage of DPNP Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study DPNP-2)



14.5 Fibromyalgia

Adult Trials in Fibromyalgia

The efficacy of CYMBALTA for the management of fibromyalgia in adults was established in two randomized, double-blind, placebo-controlled, fixed-dose trials in adult patients meeting the American College of Rheumatology criteria for fibromyalgia (a history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites). Study FM-1 was three months in duration and enrolled female patients only. Study FM-2 was six months in duration and enrolled male and female patients. Approximately 25% of participants had a comorbid diagnosis of MDD. Studies FM-1 and FM-2 enrolled a total of 874 patients of whom 541 (62%) completed the trials. A total of 354 patients (234 CYMBALTA, 120 placebo) were enrolled in Study FM-1 and a total of 520 patients (376 CYMBALTA, 144 placebo) were enrolled in Study FM-2 (5% male, 95% female). The patients had a baseline pain score of 6.5 on an 11-point scale ranging from 0 (no pain) to 10 (worse possible pain).

Studies FM-1 and FM-2 compared CYMBALTA 60 mg once daily or 120 mg daily (given in divided doses in Study FM-1 and as a single daily dose in Study FM-2) with placebo. Study FM-2 additionally compared CYMBALTA 20 mg with placebo during the initial three months of a six-month trial.

Treatment with CYMBALTA 60 mg or 120 mg daily 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. Pain reduction was observed in patients both with and without comorbid MDD. However, the degree of pain reduction may be greater in patients with comorbid MDD. For various degrees of improvement in pain from baseline to study endpoint, Figures 5 and 6 show the fraction of patients achieving that degree of improvement in Studies FM-1 and FM-2, respectively. 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 trial were assigned 0% improvement. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the trial. Improvement was also demonstrated on measures of function (Fibromyalgia Impact Questionnaires) and patient global impression of change (PGI). Neither trial demonstrated a benefit of 120 mg compared to 60 mg, and a higher dosage was associated with more adverse reactions and premature discontinuations of treatment.

Figure 5: Percentage of Adult Fibromyalgia Patients Achieving Various Levels of Pain Relief at Study Endpoint as Measured by 24-Hour Average Pain Severity (Study FM-1)

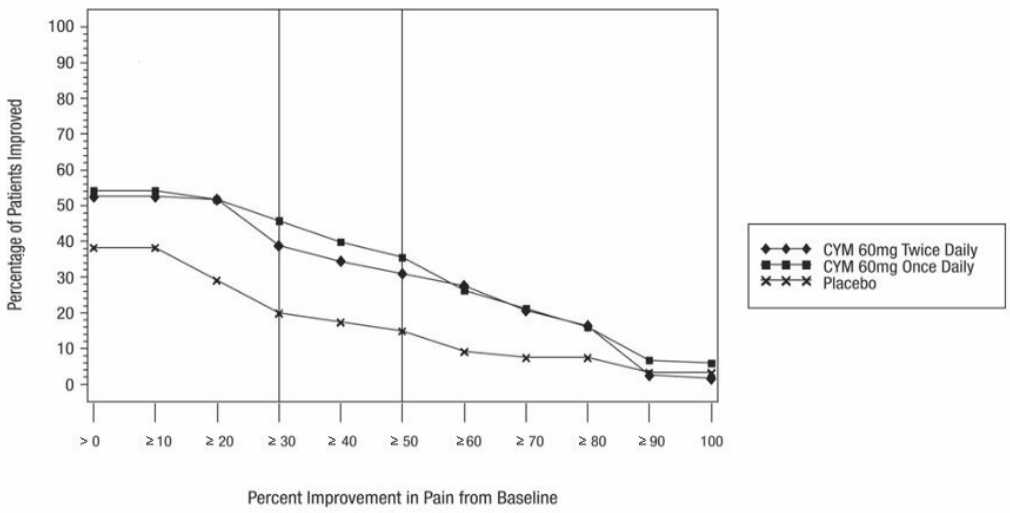
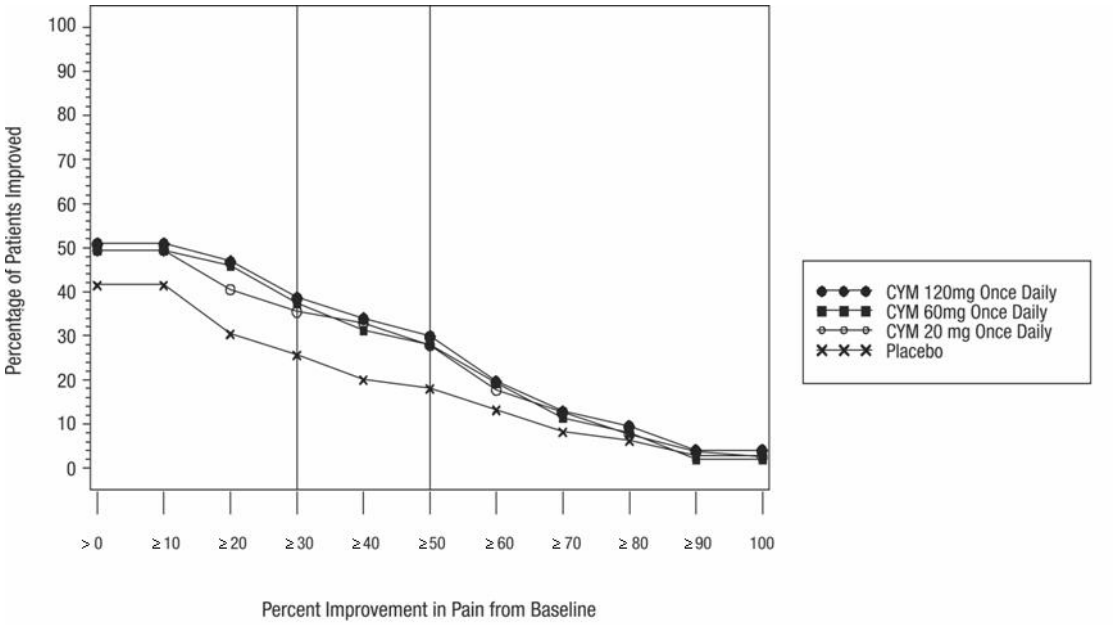


Figure 6: Percentage of Adult Fibromyalgia Patients Achieving Various Levels of Pain Relief at Study Endpoint as Measured by 24-Hour Average Pain Severity (Study FM-2)

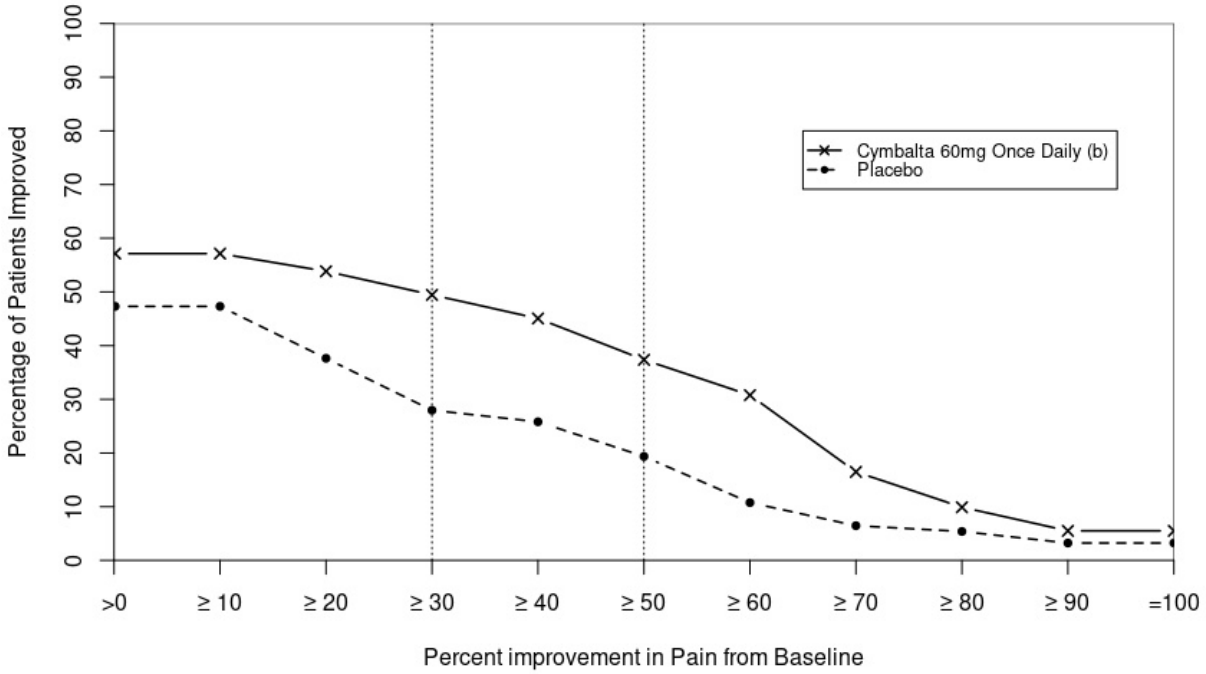


Additionally, the benefit of up-titration in non-responders to CYMBALTA at 60 mg/day was evaluated in a separate trial (Study FM-3). Adult patients were initially treated with CYMBALTA 60 mg once daily for eight weeks in open-label fashion. Subsequently, completers of this phase were randomized to double-blind treatment with CYMBALTA at either 60 mg once daily or 120 mg once daily. Responders were defined as patients who had at least a 30% reduction in pain score from baseline at the end of the 8-week treatment. Patients who were non-responders at 8 weeks were no more likely to meet response criteria at the end of 60 weeks of treatment if blindly titrated to CYMBALTA 120 mg as compared to those who were blindly continued on CYMBALTA 60 mg.

Pediatric Trial in Fibromyalgia

CYMBALTA was studied in 184 pediatric patients aged 13 to 17 years with juvenile fibromyalgia syndrome in a 13-week, placebo-controlled trial (Study FM-4). In Study FM-4, 149 (81%) patients completed the trial. CYMBALTA (N=91) was initiated at a dosage of 30 mg once daily for one week and titrated to 60 mg once daily for 12 weeks, as tolerated. The mean dosage for patients completing the 12-week treatment phase was 49 mg/day. CYMBALTA showed improvement over placebo on the primary endpoint [change from baseline to end-of-treatment on the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating] with a p-value of 0.052 from the pre-specified primary analysis, and p-values ranging from 0.011-0.020 from sensitivity analyses which assigned baseline values to missing assessments of some patients who did not complete the trial for various reasons. The patients had a baseline BPI of 5.7. For various degrees of improvement in pain from baseline to study endpoint, Figure 7 shows the fraction of patients achieving that degree of improvement in Study FM-4.

Figure 7: Percentage of Pediatric Patients Aged 13 to 17 Years Old with Juvenile Fibromyalgia Syndrome Achieving Various Levels of Pain Relief at Week 12 (Study FM-4)[a]



[a] Pain relief Measured by Brief Pain Inventory – Modified Short Form: Adolescent Version Average Pain Score.
[b] CYMBALTA-treated patients received 30 mg once daily for 1 week and subsequently titrated to 60 mg once daily for 12 weeks, as tolerated.

14.6 Chronic Musculoskeletal Pain in Adults

CYMBALTA is indicated for the treatment of chronic musculoskeletal pain in adults. This has been established in trials in adult patients with chronic low back pain and chronic pain due to osteoarthritis.

Trials in Chronic Low Back Pain in Adults

The efficacy of CYMBALTA in chronic low back pain (CLBP) in adults was assessed in two double-blind, placebo-controlled, randomized clinical trials of 13-weeks duration (Studies CLBP-1 and CLBP-2), and one of 12-weeks duration (CLBP-3). Studies CLBP-1 and CLBP-3 demonstrated efficacy of CYMBALTA in the treatment of CLBP. Patients in all trials had no signs of radiculopathy or spinal stenosis.

Study CLBP-1: Two hundred thirty-six adult patients (N=115 on CYMBALTA, N=121 on placebo) enrolled and 182 (77%) completed 13-week treatment phase. After 7 weeks of treatment, CYMBALTA-treated patients with less than 30% reduction in average daily pain and who were able to tolerate 60 mg once daily had their CYMBALTA dosage, in a double-blinded fashion, increased to 120 mg once daily for the remainder of the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking CYMBALTA 60-120 mg daily had a significantly greater pain reduction compared to patients taking placebo. Randomization was stratified by the patients' baseline NSAIDs use status. Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use.

Study CLBP-2: Four hundred and four patients were randomized to receive fixed dosages of CYMBALTA daily or a matching placebo (N=59 on CYMBALTA 20 mg, N=116 on CYMBALTA 60 mg, N=112 on CYMBALTA 120 mg, N=117 on placebo) and 267 (66%) completed the entire 13-week trial. After 13 weeks of treatment, none of the three CYMBALTA dosages showed a statistically significant difference in pain reduction compared to placebo.

Study CLBP-3: Four hundred and one patients were randomized to receive fixed doses of CYMBALTA 60 mg daily or placebo (N=198 on CYMBALTA, N=203 on placebo), and 303 (76%) completed the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 12 weeks of treatment, patients taking CYMBALTA 60 mg daily had significantly greater pain reduction compared to patients taking placebo.

For various degrees of improvement in pain from baseline to study endpoint, Figures 8 and 9 show the fraction of patients in Studies CLBP-1 and CLBP-3 achieving that degree of improvement, respectively. 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 trial were assigned the value of 0% improvement.

Figure 8: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-1)

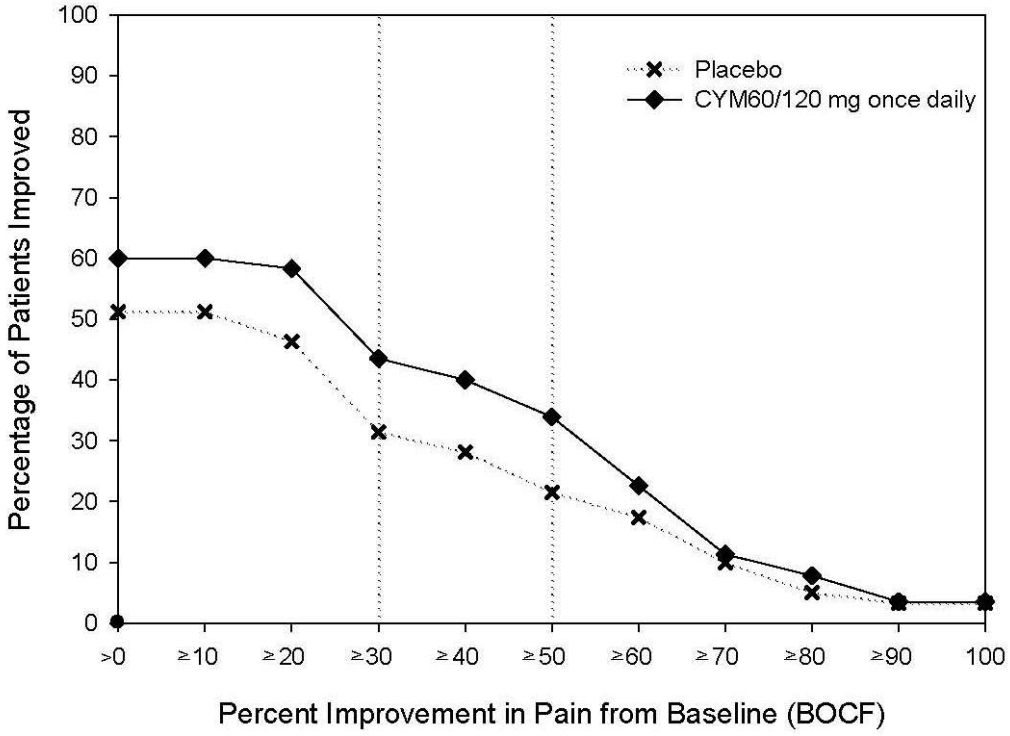
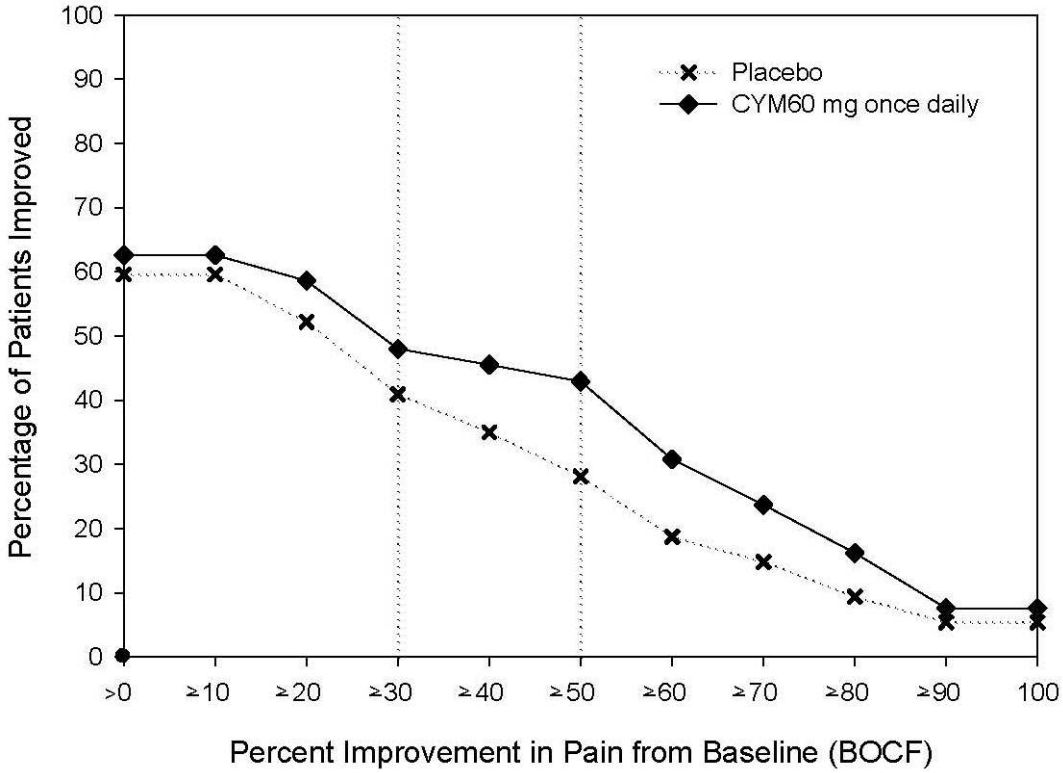


Figure 9: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-3)



Trials in Chronic Pain Due to Osteoarthritis in Adults

The efficacy of CYMBALTA in chronic pain due to osteoarthritis (OA) in adults was assessed in 2 double-blind, placebo-controlled, randomized clinical trials of 13-weeks duration (Study OA-1 and Study OA-2). All patients in both trials fulfilled the ACR clinical and radiographic criteria for classification of idiopathic OA of the knee. Randomization was stratified by the patients' baseline NSAIDs-use status.

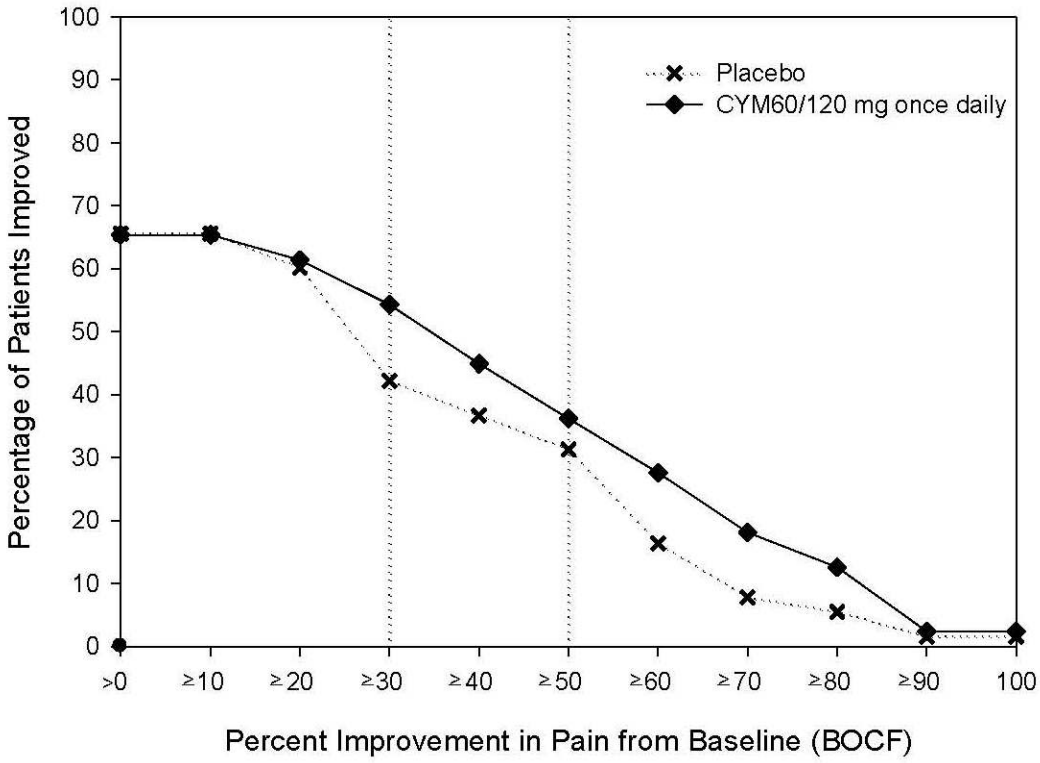
Patients assigned to CYMBALTA started treatment in both trials at a dose of 30 mg once daily for one week. After the first week, the dose of CYMBALTA was increased to 60 mg once daily. After 7 weeks of treatment with CYMBALTA 60 mg once daily, in Study OA-1 patients with sub-optimal response to treatment (<30% pain reduction) and tolerated CYMBALTA 60 mg once daily had their dose increased to 120 mg. However, in Study OA-2, all patients, regardless of their response to treatment after 7 weeks, were re-randomized to either continue receiving CYMBALTA 60 mg once daily or have their dosage increased to 120 mg once daily for the remainder of the trial. Patients in the placebo treatment groups in both trials received a matching placebo for the entire duration of trials. For both trials, efficacy analyses were conducted using 13-week data from the combined CYMBALTA 60 mg and 120 mg once daily treatment groups compared to the placebo group.

Study OA-1: Two hundred fifty-six patients (N=128 on CYMBALTA, N=128 on placebo) enrolled and 204 (80%) completed the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking CYMBALTA had significantly greater pain reduction than patients taking placebo. Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use.

Study OA-2: Two hundred thirty-one patients (N=111 on CYMBALTA, N=120 on placebo) enrolled and 173 (75%) completed the trial. Patients had a mean baseline pain of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking CYMBALTA did not show a significantly greater pain reduction than patients taking placebo.

In Study OA-1, for various degrees of improvement in pain from baseline to study endpoint, Figure 10 shows the fraction of patients achieving that degree of improvement. The figure is 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 trial were assigned the value of 0% improvement.

Figure 10: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-1)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CYMBALTA (duloxetine delayed-release capsules) is available in the following strengths, colors, imprints, and presentations:

Features	Strengths		
	20 mg[a]	**30 mg[a]**	**60 mg[a]**
Body color	Opaque green	Opaque white	Opaque green
Cap color	Opaque green	Opaque blue	Opaque blue
Cap imprint	Lilly 3235	Lilly 3240	Lilly 3270
Body imprint	20mg	30mg	60mg
Capsule number	PU3235	PU3240	PU3270
Presentations and NDC Codes			
Bottles of 30	NA	0002-3240-30	0002-3270-30
Bottles of 60	0002-3235-60	NA	NA
Bottles of 90	NA	0002-3240-90	NA
Bottles of 1000	NA	NA	0002-3270-04

[a] equivalent to duloxetine base

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Suicidal Thoughts and Behaviors — Advise patients, their families, and their caregivers to look for the emergence of suicidal ideation and behavior, especially during treatment and when the dose is adjusted up or down and instruct them to report such symptoms to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Administration — Advise patients to swallow CYMBALTA whole and to not chew, crush, or open the capsule (do not sprinkle contents on food or mixed with liquids) because these actions might affect the enteric coating.
- Hepatotoxicity — Inform patients that severe liver problems, sometimes fatal, have been reported in patients treated with CYMBALTA. Instruct patients to talk to their healthcare provider if they develop itching, right upper belly pain, dark urine, or yellow skin/eyes while taking CYMBALTA, which may be signs of liver problems. Instruct patients to talk to their healthcare provider about their alcohol consumption. Use of CYMBALTA with heavy alcohol intake may be associated with severe liver injury *[see Warnings and Precautions (5.2)]*.
- Alcohol — 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 *[see Warnings and Precautions (5.2) and Drug Interactions (7.15)]*.
- Orthostatic Hypotension, Falls and Syncope — Advise patients of the risk of orthostatic hypotension, falls and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of CYMBALTA *[see Warnings and Precautions (5.3)]*.
- Serotonin Syndrome — Caution patients about the risk of serotonin syndrome with the concomitant use of CYMBALTA and other serotonergic agents including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort *[see Contraindications (4), Warnings and Precautions (5.4), and Drug Interactions (7.14)]*. Advise patients of the signs and symptoms associated with serotonin syndrome that may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Caution patients to seek medical care immediately if they experience these symptoms.
- Increased Risk of Bleeding — Caution patients about the concomitant use of CYMBALTA and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)]*.
- Severe Skin Reactions — Caution patients that CYMBALTA may cause serious skin reactions. This may need to be treated in a hospital and may be life-threatening. Counsel patients to call their doctor right away or get emergency help if they have skin blisters, peeling rash, sores in their mouth, hives, or any other allergic reactions *[see Warnings and Precautions (5.6)]*.

- Discontinuation of Treatment — Instruct patients that discontinuation of CYMBALTA may be associated with symptoms such as dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue, and should be advised not to alter their dosing regimen, or stop taking CYMBALTA without consulting their healthcare provider *[see Warnings and Precautions (5.7)]*.
- Activation of Mania or Hypomania — Adequately screen patients with depressive symptoms for risk of bipolar disorder (e.g. family history of suicide, bipolar disorder, and depression) prior to initiating treatment with CYMBALTA. Advise patients to report any signs or symptoms of a manic reaction such as greatly increased energy, severe trouble sleeping, racing thoughts, reckless behavior, talking more or faster than usual, unusually grand ideas, and excessive happiness or irritability *[see Warnings and Precautions (5.8)]*.
- Angle-Closure Glaucoma — Advise patients that taking CYMBALTA can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle-closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.9)]*.
- Seizures — Advise patients to inform their healthcare provider if they have a history of seizure disorder *[see Warnings and Precautions (5.10)]*.
- Effects on Blood Pressure — Caution patients that CYMBALTA may cause an increase in blood pressure *[see Warnings and Precautions (5.11)]*.
- Concomitant Medications — Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions *[see Dosage and Administration (2.9, 2.10), Contraindications (4), Warnings and Precautions (5.4, 5.12), and Drug Interactions (7)]*.
- Hyponatremia — Advise patients that hyponatremia has been reported as a result of treatment with SNRIs and SSRIs, including CYMBALTA. Advise patients of the signs and symptoms of hyponatremia *[see Warnings and Precautions (5.13)]*.
- Concomitant Illnesses — Advise patients to inform their healthcare provider about all of their medical conditions *[see Warnings and Precautions (5.14)]*.
- Urinary Hesitation and Retention — CYMBALTA is in a class of medicines that may affect urination. Instruct patients to consult with their healthcare provider if they develop any problems with urine flow *[see Warnings and Precautions (5.15)]*.
- Pregnancy
  - Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with CYMBALTA.
  - Advise pregnant women or patients who intend to become pregnant that CYMBALTA use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.
  - Advise pregnant women that there is a risk of relapse with discontinuation of antidepressants.
  - Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to duloxetine during pregnancy *[see Use in Specific Populations (8.1)]*.
- Lactation — Advise breastfeeding women using CYMBALTA to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.
- Interference with Psychomotor Performance — CYMBALTA may be associated with sedation and dizziness. Therefore, caution patients about operating hazardous machinery including automobiles, until they are reasonably certain that CYMBALTA therapy does not affect their ability to engage in such activities.

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