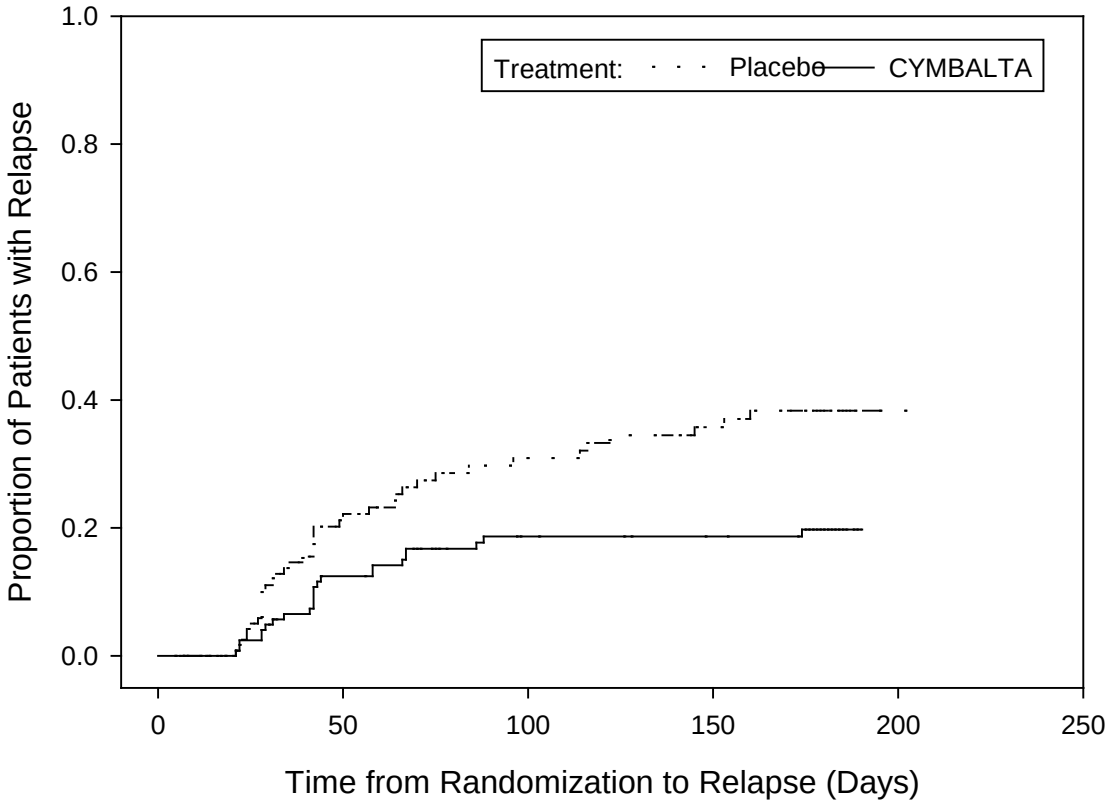
In Study MDD-5, patients on CYMBALTA experienced a statistically significantly longer time to relapse of depression than did patients on placebo (see Figure 1). Relapse was defined as an increase in the CGI-S score of ≥2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria 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

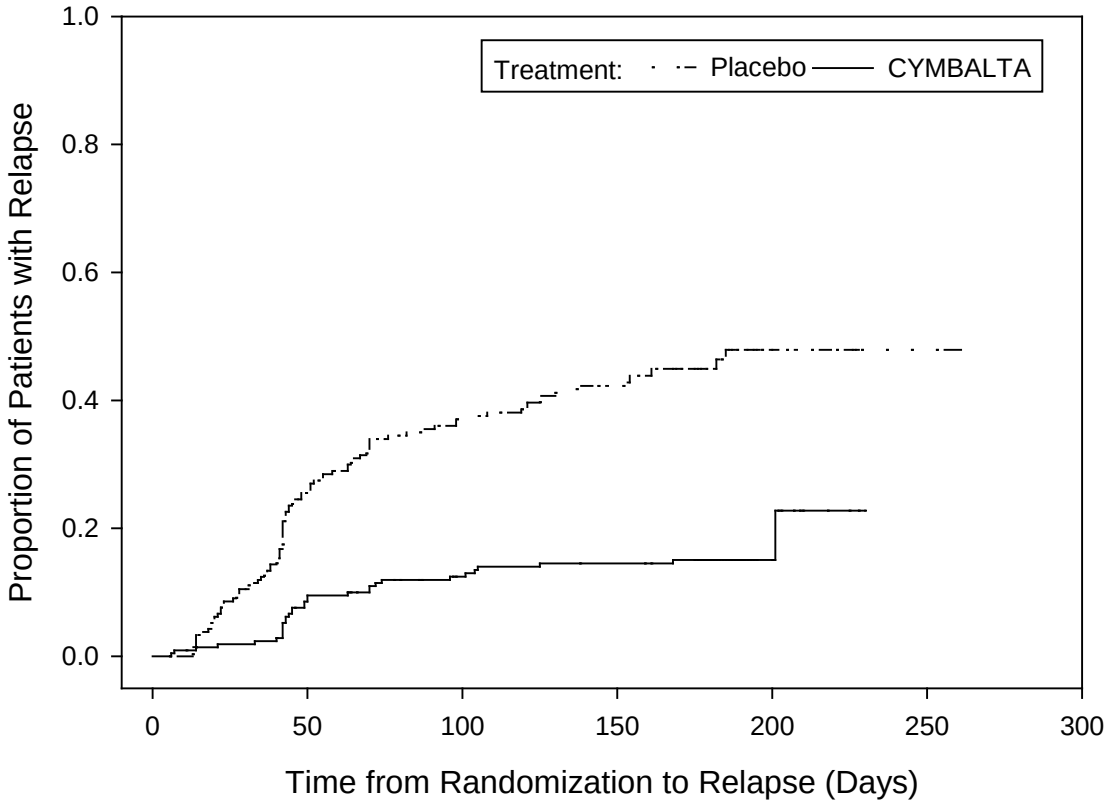
Study Number (population) (measurement)	Treatment Group	Primary Efficacy Measure		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study GAD-1 (Adult) (HAM-A)	CYMBALTA (60 mg/day)[b]	25.1 (7.18)	-12.8 (0.68)	-4.4 (-6.2, -2.5)
	CYMBALTA (120 mg/day)[b]	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)

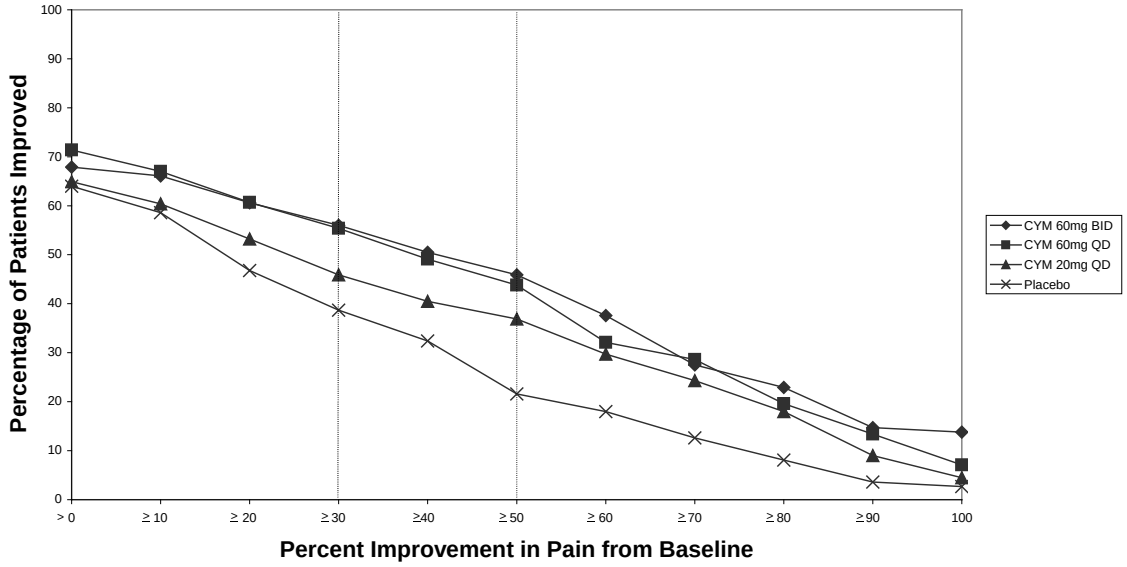
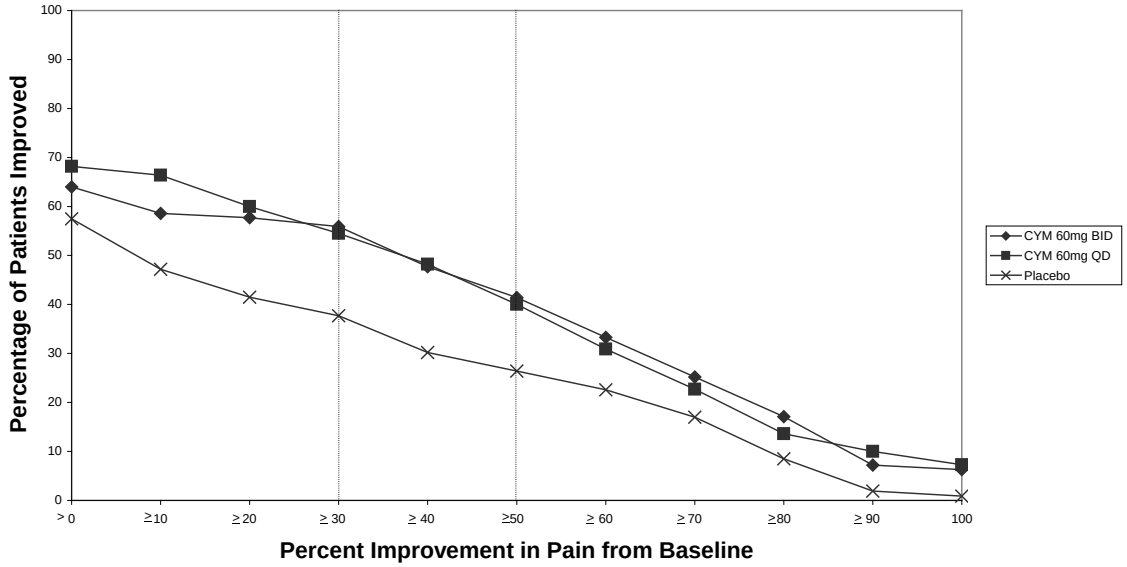


Figure 4: Percentage of DPNP Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study DPNP-2)



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)

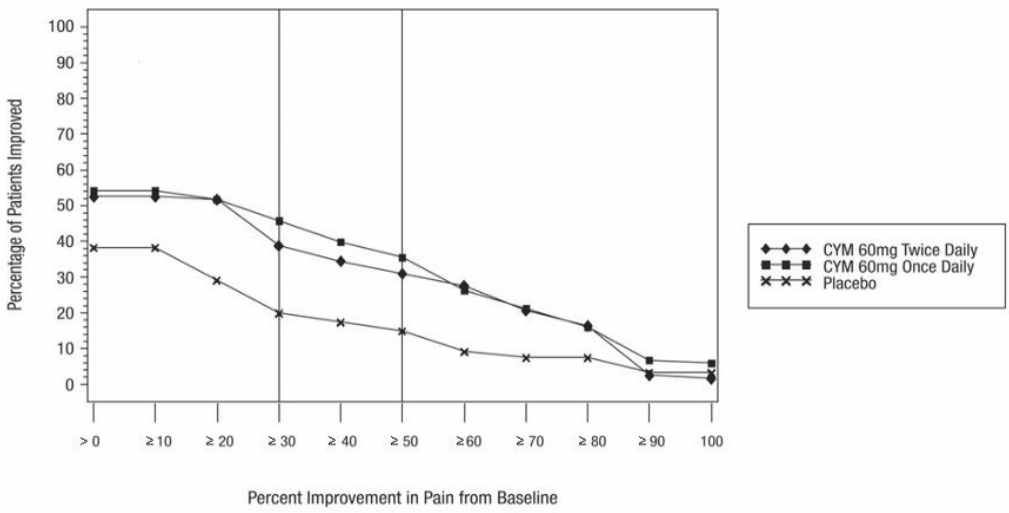
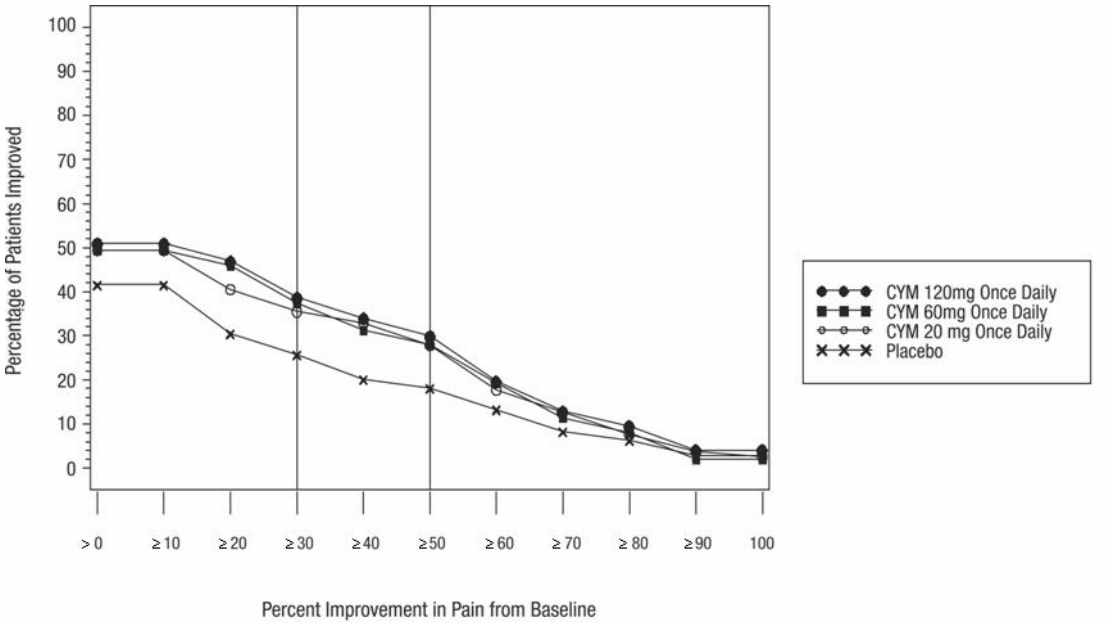


Figure 6: Percentage of Adult Fibromyalgia Patients Achieving Various Levels of Pain Relief at Study Endpoint as Measured by 24-Hour Average Pain Severity (Study FM-2)

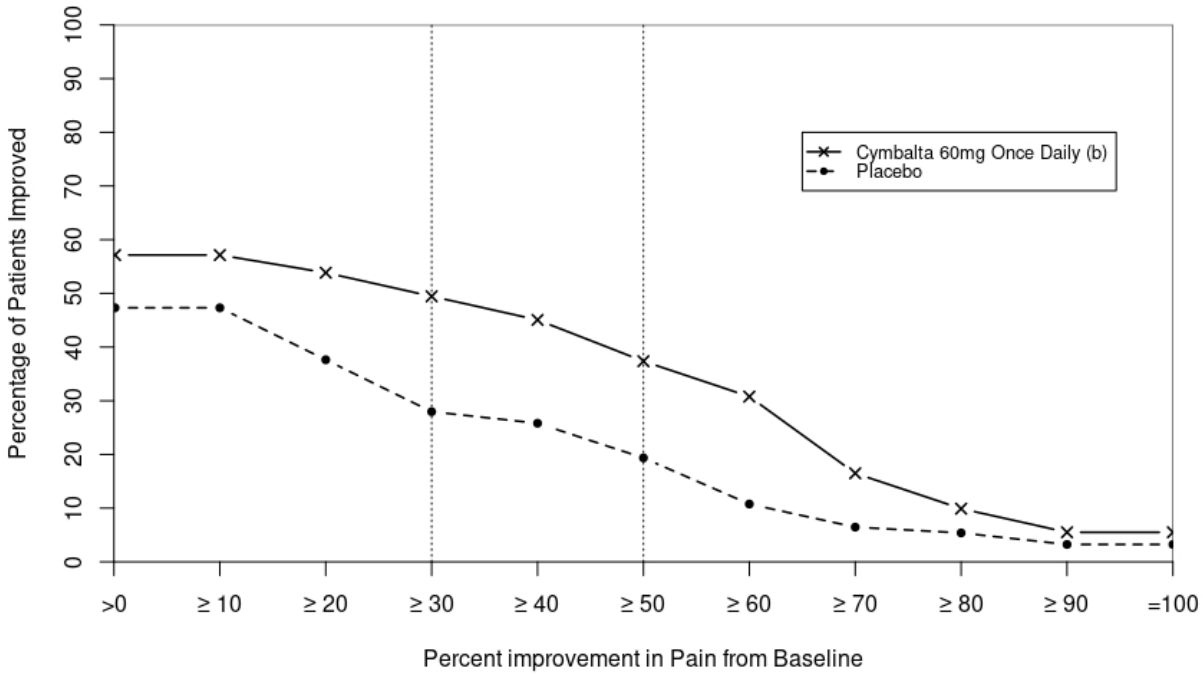


Additionally, the benefit of up-titration in non-responders to CYMBALTA at 60 mg/day was evaluated in a separate trial (Study FM-3). Adult patients were initially treated with CYMBALTA 60 mg once daily for eight weeks in open-label fashion. Subsequently, completers of this phase were randomized to double-blind 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)

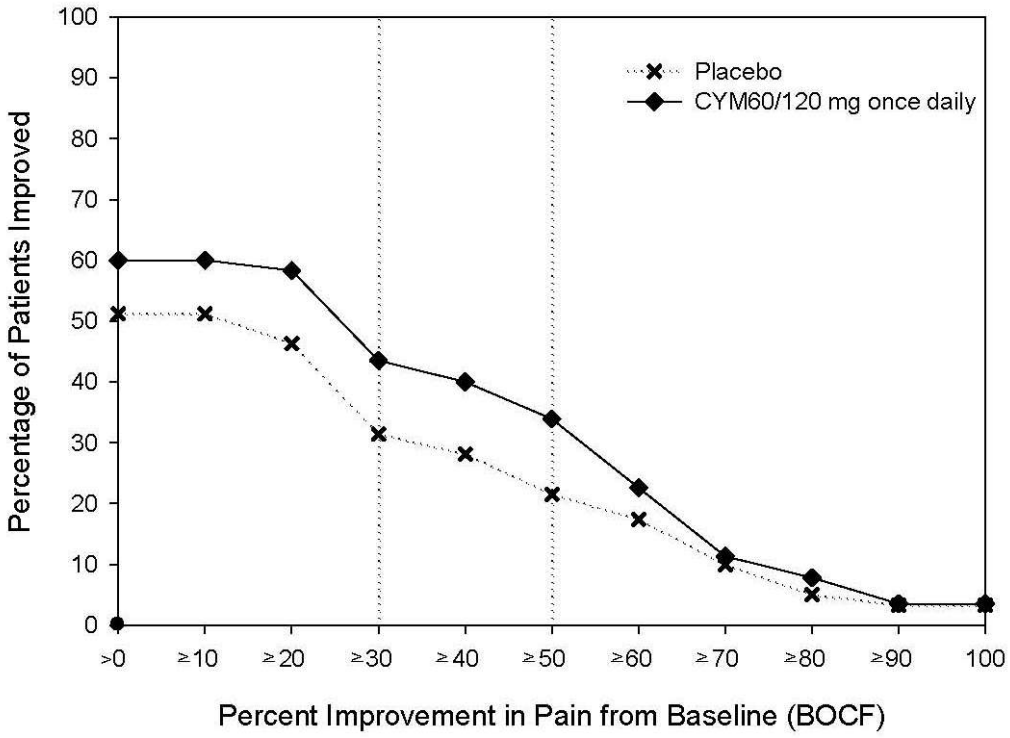
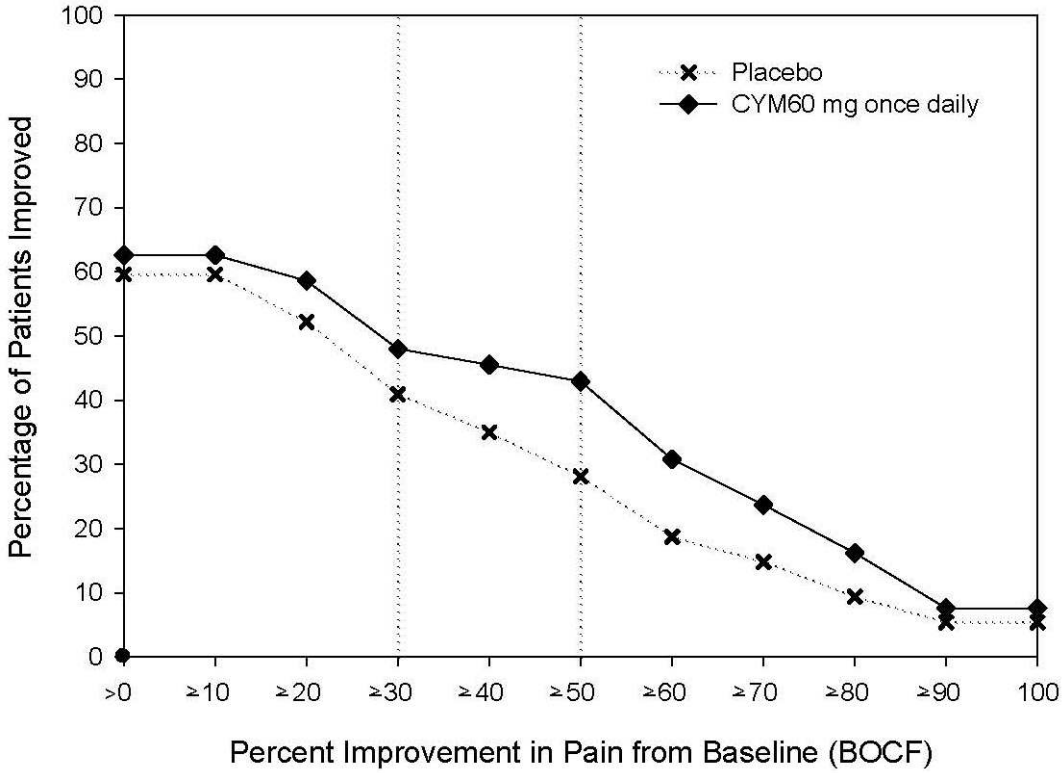


Figure 9: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-3)



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.

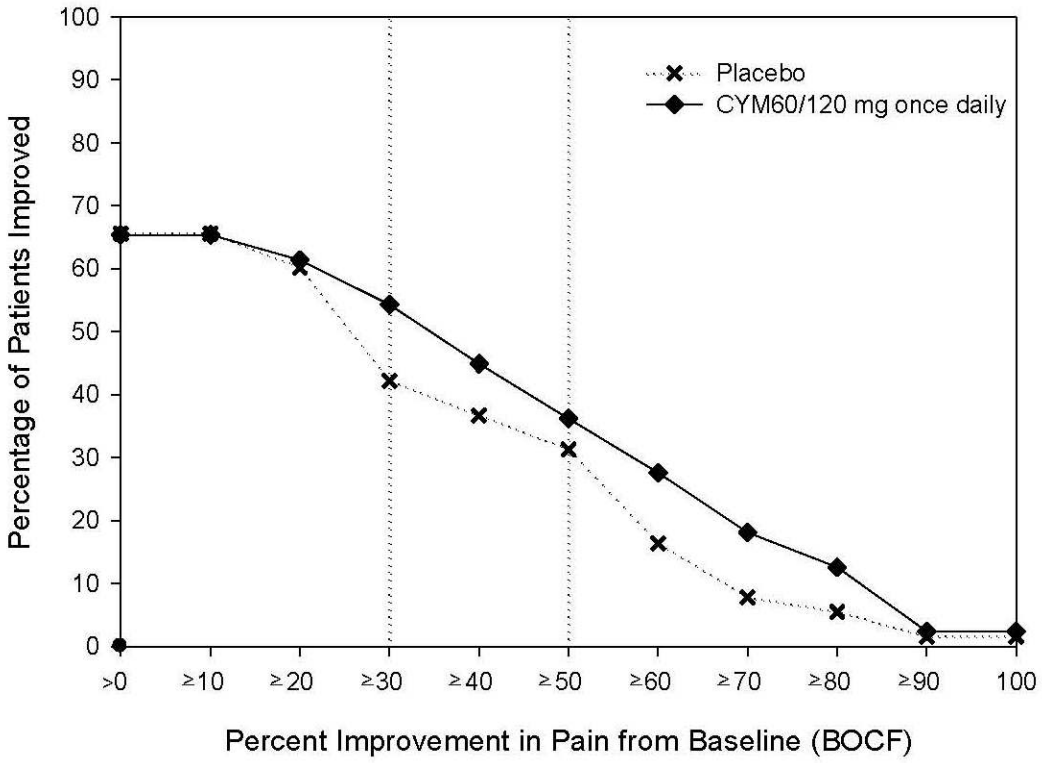
Patients assigned to CYMBALTA started treatment in both trials at a dose of 30 mg once daily for one week. After the first week, the dose of CYMBALTA was increased to 60 mg once daily. After 7 weeks of treatment with CYMBALTA 60 mg once daily, in Study OA-1 patients with sub-optimal response to treatment (<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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Medication Guide

Cymbalta®

[sim-BALL-tah]

(duloxetine delayed-release capsules)

Read this Medication Guide before you start taking Cymbalta® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Talk to your healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression, other serious mental illnesses, and suicidal thoughts or actions?

1. **Cymbalta and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment or when the dose is changed.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness).
3. **How can I watch for and try to prevent suicidal thoughts and actions?**
   - Pay close attention to any changes in mood, behavior, actions, thoughts, or feelings, especially sudden changes. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
     - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms or feelings, especially if they are new, worse, or worry you. In an emergency, call 911.

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive, being angry, or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- new or worse irritability
- trouble sleeping
- an extreme increase in activity or talking (mania)

- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to your healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show your healthcare provider. Do not start new medicines without first checking with your healthcare provider.

What is Cymbalta?

Cymbalta is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD). Cymbalta belongs to a class of medicines known as SNRIs (or serotonin-norepinephrine reuptake inhibitors).

Cymbalta is also used to treat or manage:

- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain (DPNP)
- Fibromyalgia (FM)
- Chronic Musculoskeletal Pain

Who should not take Cymbalta?

Do Not take Cymbalta if you:

- **take a Monoamine Oxidase Inhibitor (MAOI)**. Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid or intravenous methylene blue.
  - Do not take an MAOI within 5 days of stopping Cymbalta unless directed to do so by your healthcare provider.
  - Do not start Cymbalta if you stopped taking an MAOI in the last 14 days unless directed to do so by your healthcare provider.

People who take Cymbalta close in time to an MAOI may have a serious problem called Serotonin Syndrome (see "What are the possible side effects of Cymbalta?").

What should I tell my healthcare provider before taking Cymbalta?

Before starting Cymbalta, tell your healthcare provider if you:

- have heart problems or high blood pressure
- have diabetes (Cymbalta treatment makes it harder for some people with diabetes to control their blood sugar)
- have liver problems
- have kidney problems
- have glaucoma
- have or had seizures or convulsions
- have bipolar disorder or mania

- have low sodium levels in your blood
- have delayed stomach emptying
- have or had bleeding problems

- are pregnant or plan to become pregnant. Cymbalta may harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take Cymbalta during pregnancy.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Cymbalta.
  - If you become pregnant while taking Cymbalta, talk to your healthcare provider about registering with the Cymbalta Pregnancy Registry. You can register by calling 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com. The purpose of this registry is to monitor the pregnancy outcomes in women who have been treated with Cymbalta at any time during pregnancy.
- are breastfeeding or plan to breastfeed. Cymbalta passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby while taking Cymbalta.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Cymbalta and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, buspirone, SSRIs, SNRIs or MAOIs
- tramadol and fentanyl
- amphetamines
- cimetidine
- the antibiotics ciprofloxacin, enoxacin
- medicine to treat irregular heart rate (like propafenone, flecainide, quinidine)
- theophylline
- the blood thinner warfarin (Coumadin, Jantoven)
- non-steroidal anti-inflammatory drug (NSAID) (like ibuprofen, naproxen or aspirin).
- over-the-counter supplements such as tryptophan or St. John's Wort
- thioridazine (Mellaril). Mellaril together with Cymbalta can cause serious heart rhythm problems or sudden death.

Ask your healthcare provider for a list of these medicines if you are not sure.

Do not take Cymbalta with any other medicine that contain duloxetine.

How should I take Cymbalta?

- Take Cymbalta exactly as your healthcare provider tells you to take it. Your healthcare provider may need to change the dose of Cymbalta until it is the right dose for you.
- Swallow Cymbalta whole. Do not chew or crush Cymbalta.
- Do not open the capsule and sprinkle on food or mix with liquids. Opening the capsule may affect how well Cymbalta works.
- Cymbalta may be taken with or without food.

- If you miss a dose of Cymbalta, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of Cymbalta at the same time.
- If you take too much Cymbalta, call your healthcare provider or poison control center at 1-800-222-1222 right away, or get emergency treatment.
- When switching from another antidepressant to Cymbalta your healthcare provider may want to lower the dose of the initial antidepressant first to potentially avoid side effects.

What should I avoid while taking Cymbalta?

- Cymbalta can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how Cymbalta affects you.
- Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. Avoid heavy alcohol use while taking Cymbalta.

What are the possible side effects of Cymbalta?

Cymbalta may cause serious side effects, including: See “What is the most important information I should know about Cymbalta?”

Common possible side effects in people who take Cymbalta include:

1. **liver damage. Symptoms may include:**
   - itching
   - right upper abdominal pain
   - dark urine
   - yellow skin or eyes
   - enlarged liver
   - increased liver enzymes
2. **changes in blood pressure and falls.** Monitor your blood pressure before starting and throughout treatment. Cymbalta may:
   - increase your blood pressure.
   - decrease your blood pressure when standing and cause dizziness or fainting, mostly when first starting Cymbalta or when increasing the dose.
   - increase risk of falls, especially in elderly.
3. **Serotonin Syndrome: This condition can be life-threatening and symptoms may include:**
   - agitation, hallucinations, coma or other changes in mental status
   - coordination problems or muscle twitching (overactive reflexes)
   - racing heartbeat, high or low blood pressure
   - sweating or fever
   - nausea, vomiting, or diarrhea
   - muscle rigidity
   - dizziness
   - flushing
   - tremor
   - seizures

4. **abnormal bleeding:** Cymbalta and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin, Jantoven), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

5. **severe skin reactions:** Cymbalta may cause serious skin reactions that may require stopping its use. This may need to be treated in a hospital and may be life-threatening. Call your healthcare provider right away or get emergency help if you have skin blisters, peeling rash, sores in the mouth, hives or any other allergic reactions.

6. **discontinuation symptoms:** Do not stop Cymbalta without first talking to your healthcare provider. Stopping Cymbalta too quickly or changing from another antidepressant too quickly may result in serious symptoms including:
   - anxiety
   - irritability
   - feeling tired or problems sleeping
   - headache
   - sweating
   - dizziness
   - electric shock-like sensations
   - vomiting or nausea
   - diarrhea

7. **manic episodes:**
   - greatly increased energy
   - severe trouble sleeping
   - racing thoughts
   - reckless behavior
   - unusually grand ideas
   - excessive happiness or irritability
   - talking more or faster than usual

8. **visual problems:**
   - eye pain
   - changes in vision
   - swelling or redness in or around the eye

   Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

9. **seizures or convulsions**

10. **low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:
    - headache
    - weakness or feeling unsteady
    - confusion, problems concentrating or thinking or memory problems

11. problems with urination. Symptoms may include:

- decreased urine flow
- unable to pass any urine

The most common side effects of Cymbalta include:

- nausea
- dry mouth
- sleepiness
- fatigue
- constipation
- loss of appetite
- increased sweating
- dizziness

Common possible side effects in children and adolescents who take Cymbalta include:

- nausea
- decreased weight
- dizziness

Side effects in adults may also occur in children and adolescents who take Cymbalta. Children and adolescents should have height and weight monitored during treatment.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Cymbalta. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to 1-800-FDA-1088.

How should I store Cymbalta?

Store Cymbalta at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Cymbalta and all medicines out of the reach of children.

General information about the safe and effective use of Cymbalta.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Cymbalta for a condition for which it was not prescribed. Do not give Cymbalta to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Cymbalta. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about Cymbalta that is written for healthcare professionals.

For more information, call 1-800-545-5979.

What are the ingredients in Cymbalta?

Active ingredient: duloxetine hydrochloride

Inactive ingredients:

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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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